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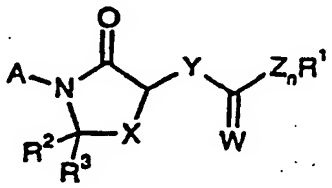
(54) Title: SUBSTITUTED PYRROLIDONE, THIAZOLIDONES OR OXAZOLIDONES AS HERBICIDES

(57) Abstract

Compounds of general formula (I), wherein X is O, S or CR^4R^5; each R^4 and R^5 is, independently, hydrogen or C_1-C_4 alkyl; Z is O, S or NR^4; n is 0 or 1; Y is O, S, NR^6 or CR^4R^5; R^6 is H, OH, CHO, $NR^{16}R^{17}$ or C_1-C_{10} hydrocarbyl, O-(C_1-C_{10} hydrocarbyl), either of which may be substituted with one orm ore substituents chosen from OR^{16}, COR^{16}, $COOR^{16}$, $OCOR^{16}$, CN, halogen, $S(O)_pR^{16}$, $NR^{16}R^{17}$, NO_2, $NR^{16}COR^{17}$, $NR^{16}CONR^{17}R^{18}$, $CONR^{16}R^{17}$ or heterocyclyl; R^{16}, R^{17} and R^{18} are each, independently, hydrogen, C_1-C_6 hydrocarbyl or C_1-C_6 halohydrocarbyl; p is 0, 1 or 2; alternatively: when Y is NR^6 or CR^4R^5, and: a) Z is NR^4; or b) n is 0; the substituents of Y and Z or Y and R^1 may together form a bridge represented by the formula $-Q^1-Q^2-$ or $-Q^1-Q^2-Q^3-$, where Q^1, Q^2 and Q^3 each independently represent $CR^{12}R^{13}$, $=CR^{12}$, CO, NR^{14}, =N, O or S; each or R^{12} and R^{13} independently represents hydrogen, C_1-C_4 alkyl, OH or halogen; R^{14} represents hydrogen or C_1-C_4 alkyl; W is O or S; R^1 is hydrogen or C_1-C_{10} hydrocarbyl or heterocyclyl having 3 to 8 ring atoms; R^2 and R^3 are each independently hydrogen or C_1-C_4 alkyl; A is an aromatic or heteroaromatic ring system optionally substituted alternatively, two or more substituents of the group A may combine to form a fused 5- or 6-membered saturated or partially saturated carbocyclic or heterocyclic ring in which any carbon or quaternised nitrogen atom may be substituted with any of the groups mentioned above for A or in which a ring carbon atom may be part of a carbonyl group or a nitrogen atom may be oxidised.



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SUBSTITUTED PYRROLIDONE, THIAZOLIDONES OR OXAZOLIDONES AS HERBICIDES

This invention relates to chemical compounds useful as herbicides, to processes for preparing them, and to herbicidal compositions and processes utilising them.

Various compounds based upon substituted nitrogen containing heterocycles are known, for example from DE-A-2212558. AU-A-8656417 also discloses compounds based upon nitrogen heterocycles and these are said to be useful as plant growth regulators. There is no mention of herbicidal activity.

The applicants have found a group of compounds which have a particular substitution pattern and which are active as herbicides.

In a first aspect of the present invention there is provided a compound of general formula I:

wherein

X is O, S or CR^4R^5;

Z is O, S or NR^4;

n is 0 or 1;

Y is O, S, NR^6 or CR^4R^5;

each R^4 and R^5 is, independently, hydrogen or C_1-C_4 alkyl;

R^6 is H, OH, CHO, $NR^{16}R^{17}$ or C_1-C_{10} hydrocarbyl, O-(C_1-C_{10} hydrocarbyl), either of which may be substituted with one or more substituents chosen from OR^{16}, COR^{16}, $COOR^{16}$, $OCOR^{16}$, CN, halogen, $S(O)_pR^{16}$, $NR^{16}R^{17}$, NO_2, $NR^{16}COR^{17}$, $NR^{16}CONR^{17}R^{18}$, $CONR^{16}R^{17}$ or heterocyclyl;

R^{16}, R^{17} and R^{18} are each, independently, hydrogen, C_1-C_6 hydrocarbyl or C_1-C_6 halohydrocarbyl;

p is 0, 1 or 2;

alternatively:

when Y is NR^6 or CR^4R^5, and:

a) Z is NR^4; or

b) n is 0;

the substituents of Y and Z or Y and R^1 may together form a bridge represented by the formula $-Q^1-Q^2-$ or $-Q^1-Q^2-Q^3-$, where Q^1, Q^2 and Q^3 each independently represent $CR^{12}R^{13}$, $=CR^{12}$, CO, NR^{14}, =N, O or S;

each of R^{12} and R^{13} independently represents hydrogen, C_1-C_4 alkyl, OH or halogen;

R^{14} represents hydrogen or C_1-C_4 alkyl;

W is O or S;

R^1 is hydrogen or C_1-C_{10} hydrocarbyl or heterocyclyl having 3 to 8 ring atoms, either of which may optionally be substituted with one or more substituents chosen from halogen (i.e. chlorine, bromine, fluorine or iodine), hydroxy, $SO_2NR^aR^b$ (where R^a and R^b are independently H or C_{1-6} alkyl), SiR^c_3 (where each R^c is independently C_1-C_4 alkyl or phenyl), cyano, nitro, amino, mono- and dialkylamino in which the alkyl groups have from 1 to 6 or more carbon atoms, acylamino, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, carboxy, carboxyamide, in which the groups attached to the N atom may be hydrogen or optionally substituted lower hydrocarbyl; alkoxy carbonyl wherein the alkoxy group may have from 1 to 6 or more carbon atoms, or aryl such as phenyl;

R^2 and R^3 are each independently hydrogen or C_1-C_4 alkyl;

A is an aromatic or heteroaromatic ring system optionally substituted with one or more substituents selected from: halogen or C_1-C_{10} hydrocarbyl, -O(C_1-C_{10} hydrocarbyl), -S(C_1-C_{10} hydrocarbyl), -SO(C_1-C_{10} hydrocarbyl) or -SO_2(C_1-C_{10} hydrocarbyl), cyano, nitro, SCN, SiR^c_3 (where each R^c is independently C_1-C_4 alkyl or phenyl), COR^7, CR^7NOR^8, NHOH, ONR^7R^8, SF_5, $COOR^7$, $SO_2NR^7R^8$, OR^9 or $NR^{10}R^{11}$; and in which any ring nitrogen atom may be quaternised or oxidised; alternatively, two or more substituents of the group A may combine to form a fused 5- or 6-membered saturated or partially saturated carbocyclic or heterocyclic ring in which any carbon or quaternised nitrogen atom may be substituted with any of the groups mentioned above for A or in which a ring carbon atom may be part of a carbonyl group or a nitrogen atom may be oxidised;

R^7 and R^8 are each independently hydrogen or C_1-C_{10} hydrocarbyl;

R^9 is hydrogen, C_1-C_{10} hydrocarbyl, SO_2(C_1-C_{10} hydrocarbyl), CHO, CO(C_1-C_{10} hydrocarbyl), COO(C_1-C_{10} hydrocarbyl) or $CONR^7R^8$;

R^{10} and R^{11} are each independently hydrogen, C_1-C_{10} hydrocarbyl, O(C_1-C_{10} hydrocarbyl), SO_2(C_1-C_{10} hydrocarbyl), CHO, CO(C_1-C_{10} hydrocarbyl), COO(C_1-C_{10} hydrocarbyl) or $CONR^7R^8$;

any of the hydrocarbyl groups within the group A may optionally be substituted with halogen (i.e. chlorine, bromine, fluorine or iodine), hydroxy, $SO_2NR^aR^b$ (where R^a and R^b are independently H or C_{1-6} alkyl), cyano, nitro, amino, mono- and dialkylamino in which the alkyl groups have from 1 to 6 or more carbon atoms, acylamino, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, carboxy, carboxyamide, in which the groups attached to the N atom may be hydrogen or lower hydrocarbyl optionally substituted with halogen; alkoxy carbonyl wherein the alkoxy group may have from 1 to 6 or more carbon atoms, or aryl such as phenyl;

provided that:

i) when A is a phenyl group or a substituted phenyl group in which no two adjacent substituents are joined to form a partially or fully saturated ring and Y is O; then Z is not NR^4;

ii) when X is S, R^2 and R^3 are both H and Y is CH_2; then the group $(Z)_n-R^1$ is other than OH, OC_{1-4} alkyl, $NHN(C_{1-2}$ alkyl$)_2$;

iii) when X is CH_2, R^2 and R^3 are both H, Y is NH or NCH_3, A is unsubstituted phenyl or phenyl substituted with halo, methoxy, CF_3 or NO_2 and n is 0; then R^1 is other than pyridyl, trimethoxyphenyl or dihalophenyl.

GB 1345159 discloses compounds which are somewhat similar to those of the present invention. It is suggested in this document that the compounds may be active as herbicides but there are few examples and no data which eluidates the degree of activity of the compounds.

WO-A-9413652, published after the priority date of the present application discloses similar compounds which also have herbicidal activity. However, there are certain differences in the structure of these prior art compounds and, in particular, the equivalent atom to Z of the present invention is always nitrogen in the compounds of this prior art document.

The expression "C_1-C_{10} hydrocarbyl" in the foregoing definitions, whether the expression is used on its own or as part of a larger radical such as, for example, C_1-C_{10} hydrocarbyloxy, is intended to include hydrocarbyl radicals of up to ten carbon atoms. Subclasses of such hydrocarbyl radicals include radicals with up to four or up to six carbon atoms. The expression "hydrocarbyl" is intended to include within its

scope aliphatic, alicyclic, and aromatic hydrocarbyl groups and combinations thereof. It thus includes, for example, alkyl, alkenyl, and alkynyl radicals, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, and cyclohexyl radicals, the adamantyl radical and the phenyl radical.

The expression "heterocyclyl" in the foregoing definitions is intended to include both aromatic and non-aromatic radicals. Examples of heteroaromatic radicals inclquiude pyridyl, pyrimidyl, triazinyl, thienyl, furyl, oxazolyl, isoxazolyl, and thiazolyl and examples of non-aromatic radicals include partially and fully saturated variants of the above.

The expression "C_1-C_6 alkyl" refers to fully saturated straight or branched hydrocarbon chains having from one to six carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl and n-hexyl. Expressions such as "alkoxy", "cycloalkyl" "alkylthio" "alkylsulphonyl", "alkylsulphinyl" and "haloalkyl" should be construed accordingly.

The expression "C_2-C_6 alkenyl" refers to a straight or branched hydrocarbon chain having from two to six carbon atoms and at least one carbon-carbon double bond. Examples include ethenyl, 2-propenyl and 2-hexenyl. Expressions such as cycloalkenyl, alkenyloxy and haloalkenyl should be construed accordingly.

The expression "C_2-C_6 alkynyl" refers to a straight or branched hydrocarbon chain having from two to six carbon atoms and at least one carbon-carbon triple bond. Examples include ethynyl, 2-propynyl and 2-hexynyl. Expressions such as cycloalkynyl, alkynyloxy and haloalkynyl should be construed accordingly.

In the context of the present specification the terms "aryl" and "aromatic ring system" refer to ring systems which may be mono-, bi- or tricyclic. Examples of such rings include phenyl, naphthalenyl, anthracenyl or phenanthrenyl. Nitrogen atoms in the ring may be quaternised or oxidised.

In the context of the present specification, the term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom and consisting either of a single ring or of two or more fused rings.

Preferably, single rings will contain up to four and bicyclic systems up to five heteroatoms which will preferably be chosen from nitrogen, oxygen and sulphur. Examples of such groups include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3,4-thiatriazolyl, 1,2,3,5-thiatriazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,4,5-tetrazinyl, benzofuryl, benzisofuryl, benzothienyl, benzisothienyl, indolyl, isoindolyl, indazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, benzotriazinyl, purinyl, pteridinyl and indolizinyl.

In the context of the present specification, the term "fused saturated or partially saturated carbocyclic or heterocyclic ring" refers to a ring system in which a 5- or 6- membered carbocyclic or heterocyclic ring which is not of aromatic character is fused to an aromatic or heteroaromatic ring system. Examples of such systems include benzimidazolinyl, benzoxazolinyl and benzodioxolyl.

Examples of particular values for substituents of the group A include methyl, ethyl, n-propyl, iso-propyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, ethoxyvinyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, n-propoxy, iso-propoxy, difluoromethoxy, trifluoromethoxy, tetrafluoroethoxy, cyano, nitro, amino, mono- or dialkylamino in which each alkyl group may have from 1 to 6 or more carbon atoms, hydroxylamino, acyl (e.g. acetyl or trifluoroacetyl), methylthio, methylsulphinyl, methylsulphonyl, trifluoromethylthio, SCN, SF_5, trifluoromethylsulphinyl, trifluoromethylsulphonyl, sulphonamido, carboxy, alkoxycarbonyl in which the alkoxy group may have from 1 to 6 or more carbon atoms, carboxyamide in which the groups attached to the N atom may be hydrogen or optionally substituted lower hydrocarbyl; or acylamino (e.g. acetamido). When there is more than one substituent, the substituents may be the same or different.

Preferred substituents of the group A include C_1-C_4 alkyl, C_1-C_4 haloalkyl, O(C_1-C_4 alkyl), O(C_1-C_4 haloalkyl), S(C_1-C_4 alkyl), S(C_1-C_4 haloalkyl) and halo. Specific examples of these preferred substituents are trifluoromethyl, trichloromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, dichloromethoxy, fluoromethoxy, chloromethoxy,

trichloroethoxy, trifluoroethoxy, dichloroethoxy, difluoroethoxy, fluoroethoxy, trifluoromethylthio, ethoxy, methoxy, fluoro, chloro, bromo, iodo and methyl.

Preferred compounds include those in which R^1 is hydrogen or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, CO(C_1-C_6 alkyl), CO(C_2-C_6 alkenyl), CO(C_2-C_6 alkynyl), C_3-C_8 cycloalkyl, benzyl, phenyl or a 5 or 6 membered heterocyclic ring. Any of these R^1 groups may be substituted with one or more substituents chosen from halo, SiR^c_3, CN, COOH, COO(C_1-C_4 alkyl), CON(C_1-C_4 alkyl)$_2$ or CO(C_1-C_4 alkyl) and cycloalkyl, benzyl, phenyl or heterocyclic R^1 groups may, additionally, be substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl.

Specific examples of preferred groups R^1 include optionally substituted C_1-C_6 alkyl, for example methyl, $-C(CH_3)_3$, $-CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2CH_3$, $C(CH_3)_2CN$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $CH_2C(CH_3)_2$ or $C(CH_3)_2CH_2Cl$; C_2-C_6 alkenyl, for example $C(CH_3)_2CH{=}CH_2$ and $CH_2C(CH_3)_2CH{=}CH_2$; alkynyl, for example $CH_2C{\equiv}CH$ or $C(CH_3)_2C{\equiv}CH$; C_1-C_6 alkyl-OH, for example $C(CH_3)_2CH_2OH$; optionally substituted C_3-C_8 cycloalkyl, for example cyclobutyl, 1-methylcyclobutyl, 1-methylcyclopropyl, 1-methylcyclopentyl, 1-methylcyclohexyl, 1-cyanocyclopropyl, 1-cyanocyclobutyl, 1-cyanocyclopentyl, 1-cyanocyclohexyl, 1-acetylenylcyclopropyl, 1-acetylenylcyclobutyl, 1-acetylenylcyclopentyl, 1-acetylenylcyclohexyl; optionally substituted phenyl; optionally substituted heterocyclyl, for example pyrrolyl, methylisoxazolyl or methylpyridyl; COC_1-C_6 alkyl, for example $COC(CH_3)_3$; C_1-C_6 alkylCOO(C_1-C_4 alkyl), for example $C(CH_3)_2COOC_2H_5$; or SiR^c_3, for example trimethylsilyl.

Other preferred compounds are those in which, independently or in any combination:

X is S, O or CH_2

Y is S, O, CH_2, $CH(CH_3)$ or NR^6;

Z is NH or O; or n is O and Z is not present;

R^2 and R^3 are both hydrogen; or

Q^1, Q^2 and Q^3, when present are CH_2 or C=O.

When Y is a group NR^6, it is preferred that R^6 is hydrogen, -CHO, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, for

example benzyl which is optionally substituted with C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy, (C_1-C_6 alkyl)aryl, (C_1-C_6 alkyl)heterocyclyl, -O(C_1-C_6 alkyl), -O(C_1-C_6 alkyl)aryl, -O(C_1-C_6 alkyl)heterocyclyl, -C_1-C_6 alkyl-OH, -(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-S-(C_1-C_6 alkyl), -C_1-C_6 alkyl(OC_1-C_6 alkyl)$_2$, -C_1-C_6 alkyl-NH(C_1-C_6 alkyl), -C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl-COO(C_1-C_6 alkyl), -C_1-C_6 alkyl-OCONH(C_1-C_6 alkyl) and -C_1-C_6 alkyl-OCO(C_1-C_6 alkyl).

Examples of such preferred R^6 groups include hydrogen, CHO, methyl, ethyl, isopropyl, n-propyl, isobutyl, cyclopropyl, CH_2-cyclopropyl, benzyl, substituted benzyl, for example p-trifluoromethoxybenzyl, phenyl, methoxy, 2-hydroxyethyl, 2-methoxyethyl, 2,2-dimethoxyethyl, 3-propen-1-yl, 3-propyn-1-yl, 2-(N,N-dimethylamino)ethyl, $CH_2CO_2CH_3$, $CH_2CO_2CH_2CH_3$, $CH_2CH_2OCONHC(CH_3)_3$, $CH_2CH_2COOCH_2CH_3$, 2-acetoxyethyl and 2-thiomethylethyl.

The formula I given above is intended to include tautomeric forms of the structure drawn, as well as physically distinguishable modifications of the compounds which may arise, for example, from different ways in which the molecules are arranged in a crystal lattice, or from the inability of parts of the molecule to rotate freely in relation to other parts, or from geometrical isomerism, or from intra-molelcular or inter-molecular hydrogen bonding, or otherwise.

Some of the compounds of the invention can exist in enantiomeric or diastereomeric forms. The invention includes all individual forms and mixtures thereof in all proportions.

Particular examples of compounds of general formula I are listed in Table I. In all of these compounds, both R^2 and R^3 are hydrogen. In Table I, and throughout the specification, Me represents methyl, Et represents ethyl, Pr represents propyl, Ph represents phenyl, Bz represents benzyl and Ac represents acetyl.

TABLE I

Comp	Prep.	A	X	Y	(Z)n	R1	W
1	Ex 1	m-CF3 Ph	S	NH	NH	C(Me)3	O
2	Ex 2	m-CF3 Ph	S	NH	O	CH(Me)2	O
3	Ex 3	m-CF3 Ph	S	NH	"	C(Me)3	O
4	Ex 4	m-CF3 Ph	S	O	"	C(Me)3	O
5	Ex 5	m-CF3 Ph	S	O	"	CH2C(Me)3	O
6	Ex 6	m-CF3 Ph	S	CH2	NH	C(Me)3	O
7	Ex 7	m-CF3 Ph	CH2	CH2	O	C(Me)3	O
8	Ex 8	m-CF3 Ph	CH2	CH2	NH	C(Me)3	O
9	Ex 9	m-CF3 Ph	CH2	O	"	pyrrol-2-yl	O
10	Ex 10	m-CF3 Ph	CH2	NCH3	NH	C(Me)3	O
11	Ex 11	m-CF3 Ph	CH2	CH2	NH	3-methyl-isoxazol-5-yl	O
12	Ex 12	m-CF3 Ph	CH2	CH2	NH	C(Me)2CH2OH	O
13	Ex 13	m-CF3 Ph	CH2	CH2	O	H	O
14	Ex 14	m-CF3 Ph	S	CH2	O	H	O
15	ex 15	m-CF3 Ph	O	CH2	O	Et	O
16	ex 8	m-CF3 Ph	CH2	CH2	NH	C(Me)2CCH	O
17	ex 16	m-CF3 Ph	CH2	CH2	NH	C(Me)2Et	O
18	ex 16	m-CF3 Ph	CH2	CH2	NH	C(Me)2CH=CH2	O
19	ex 27	m-CF3 Ph	CH2	NEt	NH	C(Me)3	O
20	ex 10	m-CF3 Ph	CH2	NMe	NH	C(Me)2CCH	O
21	ex 17	m-CF3 Ph	O	CH2	NH	C(Me)3	O
22	ex 8	m-CF3 Ph	CH2	CH2	NH	Ph	O
23	ex 8	m-CF3 Ph	CH2	CH2	NH	Et	O
24	ex 18	m-CF3 Ph	CH2	CH2	NH	cyclobutyl	O
25	ex 18	m-CF3 Ph	CH2	CH2	NH	C(Me)2COOEt	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
26	ex 12	m-CF3 Ph	CH2	CH2	NH	6-Methyl-pyrid 2 yl	O
27	ex 12	m-CF3 Ph	CH2	CH2	O	CH2CCH	O
28	ex 1	m-CF3 Ph	CH2	NH	NH	C(Me)3	O
29	ex 5	m-CF3 Ph	CH2	NH	-	CH2C(Me)3	O
30	ex 12	m-CF3 Ph	CH2	CH2	NH	COC(Me)3	O
31	ex 8	m-CF3 Ph	CH2	CH2	NH	C(Et)2CCH	O
32	ex 19	m-CF3 Ph	CH2	CHMe	NH	C(Me)3	O
33	ex 12	m CF3 Ph	CH2	CH2	NH	3-(1-ethyl 1 methylpropyl) isoxazol-5-yl	O
34	ex 16	m-CF3 Ph	CH2	NMe	NH	C(Me)2Et	O
35	ex 16	m-CF3 Ph	CH2	NMe	NH	C(Me)2CH=CH2	O
36	ex 10	m-OCF3 Ph	CH2	NMe	NH	C(Me)3	O
37	ex 10	m-CF3 Ph	CH2	NMe	NH	Ph	O
38	ex 27	m-CF3 Ph	CH2	NCH(Me)2	NH	C(Me)3	O
39	ex 17	m-CCl3 Ph	O	CH2	NH	C(Me)2CCH	O
40	ex 17	m-CF3 Ph	O	CH2	NH	C(Me)2CCH	O
41	ex 20	m-OCF3 Ph	CH2	S	NH	C(Me)3	O
42	ex 20	m-CF3 Ph	CH2	S	NH	C(Me)3	O
43	ex 10	m-SCF3 Ph	CH2	NMe	NH	C(Me)2CCH	O
44	ex 10	m-SCF3 Ph	CH2	NMe	NH	C(Me)3	O
45	ex 15	m-OCF3 Ph	O	CH2	O	Et	O
46	ex 16	m-CCl3 Ph	O	CH2	NH	C(Me)2Et	O
47	ex 16	m-CF3 Ph	O	CH2	NH	C(Me)2Et	O
48	ex 16	m-CCl3 Ph	O	CH2	NH	C(Me)2CH=CH2	O
49	ex 16	m-CF3 Ph	O	CH2	NH	C(Me)2CH=CH2	O
50	ex 17	m-OCF3 Ph	O	CH2	NH	C(Me)3	O
51	ex 5	m OCF3 Ph	CH2	NMe	-	CH2C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
52	ex 10	m-OCF3 Ph	CH2	NMe	NH	C(Me)2CCH	O
53	ex 1	m-OCF3 Ph	CH2	NH	NH	C(Me)3	O
54	ex 5	m-OCF3 Ph	CH2	NH	-	CH2C(Me)3	O
55	ex 1	m-OCF3 Ph	CH2	NH	NH	C(Me)2CCH	O
56	ex 16	m-OCF3 Ph	CH2	NMe	NH	C(Me)2Et	O
57	ex 16	m-OCF3 Ph	CH2	NH	NH	C(Me)2Et	O
58	ex 21	m-OCF3 Ph	CH2	NMe	O	C(Me)3	O
59	ex 21	m-OCF3 Ph	CH2	NH	O	C(Me)3	O
60	ex 10	m-Cl Ph	CH2	NMe	NH	C(Me)3	O
61	ex 21	m-CF3 Ph	CH2	NMe	O	C(Me)3	O
62	ex 15	m-OCHF2 Ph	O	CH2	O	Et	O
63	ex 5	m-CF3 Ph	CH2	NMe	-	CH2C(Me)3	O
64	ex 27	m-OCF3 Ph	CH2	NEt	NH	C(Me)3	O
65	ex 27	m-OCF3 Ph	CH2	NEt	NH	C(Me)2CCH	O
66	ex 17	m-OCHCl2 Ph	O	CH2	O	Et	O
67	ex 17	m-OCHCl2 Ph	O	CH2	NH	C(Me)3	O
68	ex 17	m-OCCl3 Ph	O	CH2	NH	C(Me)2CCH	O
69	ex 21	m-CF3 Ph	CH2	NH	O	C(Me)3	O
70	ex 10	m-OCHF2 Ph	CH2	NMe	NH	C(Me)3	O
71	ex 10	m-OCHF2 Ph	CH2	NMe	NH	C(Me)2CCH	O
72	ex 5	m-OCHF2 Ph	CH2	NMe	-	CH2C(Me)3	O
73	ex 21	m-OCHF2 Ph	CH2	NMe	O	C(Me)3	O
74	ex 16	m-OCHF2 Ph	CH2	NMe	NH	C(Me)2Et	O
75	ex 20	m-CF3 Ph	CH2	S	NH	C(Me)2CCH	O
76	ex 20	m-OCF3 Ph	CH2	S	NH	C(Me)2CCH	O
77	ex 22	m-OCF3 Ph	CH2	O	O	C(Me)3	O
78	ex 27	m-OCF3 Ph	CH2	N-Pr	NH	C(Me)3	O
79	ex 16	m-OCF3 Ph	CH2	S	NH	C(Me)2Et	O
80	ex 16	m-OCF3 Ph	CH2	S	NH	C(Me)2Et	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
81	ex 22	m-OCF3 Ph	CH2	NOMe	O	C(Me)3	O
82	ex 27	m-OCF3 Ph	CH2	NCH2CH2OH	NH	C(Me)3	O
83	ex 27	m-CF3 Ph	CH2	NPh	NH	C(Me)3	O
84	ex 27	m-CF3 Ph	CH2	NCH2CH2OMe	NH	C(Me)3	O
85	ex 27	m-CF3 Ph	CH2	N-cyclopropyl	NH	C(Me)3	O
86	ex 24	m-CF3 Ph	CH2	NOMe	NH	C(Me)3	O
87	ex 27	m-CF3 Ph	CH2	NCH2Ph	NH	C(Me)3	O
88	ex 24	m-OCHF2 Ph	CH2	NOMe	NH	C(Me)3	O
89	ex 5	m-CF3 Ph	CH2	NOMe	-	CH2C(Me)3	O
90	ex 27	m-OCF3 Ph	CH2	NCH2CH(OMe)2	NH	C(Me)3	O
91	ex 27	m-OCF3 Ph	CH2	NCH2CCH	NH	C(Me)3	O
92	ex 27	m-OCF3 Ph	CH2	NCH2CH2N(Me)2	NH	C(Me)3	O
93	ex 27	m-OCF3 Ph	CH2	NCH2CHCH2	NH	C(Me)3	O
94	ex 26	m-OCHF2 Ph	CH2	NMe	NH	C(Me)3	S
95	ex 26	m-CF3 Ph	CH2	NMe	NH	C(Me)3	S
96	ex 5	m-OCF3 Ph	CH2	NPr	-	CH2C(Me)3	O
97	ex 5	m-OCF3 Ph	CH2	NEt	-	CH2C(Me)3	O
98	ex 16	m-OCF3 Ph	CH2	NEt	NH	C(Me)2Et	O
99	ex 23	m-CF3 Ph	CH2	NCH2CO2Et	NH	C(Me)3	O
100	ex 26	m-OCF3 Ph	CH2	NMe	NH	C(Me)3	S
101	ex 27	m-OCF3 Ph	CH2	NCH2CH(OMe)2	NH	C(Me)CCH	O
102	ex 5	m-OCF3 Ph	CH2	NCH2CCH	-	CH2C(Me)3	O
103	ex 5	m-OCF3 Ph	CH2	NCH2CHCH2	-	CH2C(Me)3	O
104	ex 5	m-CF3 Ph	CH2	NPr	-	CH2C(Me)3	O
105	ex 27	m-CF3 Ph	CH2	NPr	NH	C(Me)3	O
106	ex 27	m-OCHF2 Ph	CH2	NPr	NH	C(Me)3	O
107	ex 26	m-OCHF2 Ph	CH2	NPr	NH	C(Me)3	S
108	ex 27	m-CF3 Ph	CH2	NCH2CHCH2	NH	C(Me)3	O
109	ex 26	m-CF3 Ph	CH2	NCH2CHCH2	NH	C(Me)3	S

Comp	Prep.	A	X	Y	(Z)n	R1	W
110	ex 5	m-OCHF2 Ph	CH2	NCH2CHCH2	-	CH2C(Me)3	O
111	ex 27	m-OCHF2 Ph	CH2	NCH2CHCH2	NH	C(Me)3	O
112	ex 26	m-OCF3 Ph	CH2	NCH2CHCH2	NH	C(Me)3	S
113	ex 5	m-OCF3 Ph	CH2	NCH2CH2N(Me)2	-	CH2C(Me)3	O
114	ex 26	m-OCF3 Ph	CH2	NEt	NH	C(Me)3	S
115	ex 26	m-OCF3 Ph	CH2	NH	NH	C(Me)3	S
116	ex 27	m-OCF3 Ph	CH2	NPr	NH	C(Me)2CCH	O
117	ex 28	m-OCF3 Ph	CH2	NCH2CH2OAc	NH	C(Me)3	O
118	ex 16	m-OCF3 Ph	CH2	NPr	NH	C(Me)2Et	O
119	ex 23	m-OCF3 Ph	CH2	NCH2CO2Me	NH	C(Me)3	O
120	ex 27	m-OCF3 Ph	CH2	NBu	NH	C(Me)3	O
121	ex 27	m-OCF3 Ph	CH2	NCH2CH2OMe	NH	C(Me)3	O
122	ex 27	m-OCF3 Ph	CH2	NCH2CH2SMe	NH	C(Me)3	O
123	ex 25	m-OCF3 Ph	CH2	NCHO	-	CH2C(Me)3	O
124	ex 10	m-CF3 Ph	S	NMe	NH	C(Me)3	O
125	ex 5	m-CF3 Ph	S	NMe	-	CH2C(Me)3	O
126	ex 5	m-CF3 Ph	S	NOMe	-	CH2C(Me)3	O
127	ex 20	m-CF3 Ph	S	S	NH	C(Me)3	O
128	ex 29	m-CF3 Ph	CH2	NCH2CO-	N-	C(Me)3	O
129	ex 30	m-OCF3 Ph	CH2	NCOCO-	N	C(Me)2CCH	O
130	ex 31	m-OCF3 Ph	CH2	NCH=CH-	N-	C(Me)2CCH	O
131	ex 32	m-CF3 Ph	CH2	NCOCH2-	N-	C(Me)3	O
132	ex 33	m-CF3 Ph	CH2	NCH2OCH2-	N-	C(Me)3	O
133	ex 30	m-OCF3 Ph	CH2	NCOCO-	N-	C(Me)3	O
134	ex 33	m-OCF3 Ph	CH2	NCH2OCH2-	N-	C(Me)3	O
135	Ex 34	m-CF3 Ph	O	O	NH	C(Me)3	O
136	Ex 35	5 trifluoromethyl-1,3,4-thiadiazol-2-yl	S	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
137	Ex 36	5-methyl-1,3,4-thiadiazol-2-yl	S	O	NH	C(Me)3	O
138	Ex 37	6-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)3	O
139	Ex 38	6-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)2CCH	O
140	Ex 39	6-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)2CH=CH2	O
141	Ex 40	4,6-bis-trifluoro-methyl pyridin-2-yl	S	O	NH	C(Me)3	O
142	Ex 41	5-trifluoromethyl-pyridin-3-yl	S	O	NH	C(Me)3	O
143	Ex 42	2-trifluoromethyl-pyridin-4-yl	S	O	NH	C(Me)3	O
144	Ex 43	4-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)3	O
145	Ex 44	4-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)2CCH	O
146	Ex 45	4-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)2Et	O
147	Ex 45	4-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)2CH=CH2	O
148	Ex 46	4-methoxypyridin-3-yl	CH2	O	NH	C(Me)3	O
149	Ex 47	4,6-dimethyl-pyrimidin-2 yl	S	O	NH	C(Me)3	O
150	Ex 48	5-bromothiazol-2-yl	S	O	NH	C(Me)3	O
151	Ex 49	4-chloro-benzothiazol-2-yl	S	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
152	Ex 50	2-chlorothien-4-yl	CH2	O	NH	C(Me)3	O
153	Ex 51	pyridin-3-yl	S	O	NH	C(Me)3	O
154	Ex 52	pyrazin-2-yl	S	O	NH	C(Me)3	O
155	Ex 53	5-trifluoromethyl-pyridin-2-yl	S	O	NH	C(Me)3	O
156	Ex 54	4-trifluoromethyl-pyrimidin-2-yl	S	O	NH	C(Me)3	O
157	Ex 55	6-trifluoromethyl-pyrimidin-4-yl	S	O	NH	C(Me)3	O
158	Ex 56	2,6-bis-trifluoro-methylpyridin-4-yl	S	O	NH	C(Me)3	O
159	Ex 57	2,2-difluoro-1,3-benzodioxol-5-yl	S	O	NH	C(Me)2CCH	O
160	Ex 58	2,2-difluoro-1,3-benzodioxol-5-yl	S	O	NH	C(Me)3	O
161	Ex 59	2,6-dichloropyridin-4-yl	CH2	O	NH	C(Me)3	O
162	Ex 60 Ex 62	4-trifluoromethyl-pyridin-2-yl	CH2	O	NH	C(Me)3	O
163	Ex 61	4-trifluoromethyl-thiazol-2-yl	CH2	O	NH	C(Me)3	O
164	Ex 61 Ex 66	6-trifluoromethyl-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
165	Ex 61	5-trifluoromethyl-1,3,4-thiadiazol-2-yl	CH2	O	NH	C(Me)3	O
166	Ex 63	2-trifluoromethyl-pyridin-4-yl	CH2	O	NH	C(Me)3	O
167	Ex 63	2-chloropyridin-4-yl	CH2	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
168	Ex 63	4-chloropyridin-2-yl	CH2	O	NH	C(Me)3	O
169	Ex 63	2-iodopyridin-4-yl	CH2	O	NH	C(Me)3	O
170	Ex 63	4,6-bistrifluoro-methylpyridin-2-yl	CH2	O	NH	C(Me)3	O
171	Ex 63	6-chloro-4-trifluoromethyl-pyridin-2-yl	CH2	O	NH	C(Me)3	O
172	Ex 64	pyridin-3-yl	CH2	O	NH	C(Me)3	O
173	Ex 65	pyridin-3-yl N-oxide	CH2	O	NH	C(Me)3	O
174	Ex 66	4-trifluoromethyl-pyrimidin-2-yl	CH2	O	NH	C(Me)3	O
175	Ex 66	pyrimidin-5-yl	CH2	O	NH	C(Me)3	O
176	Ex 66	pyrazin-2-yl	CH2	O	NH	C(Me)3	O
177	Ex 66	6-chloropyrimidin-4-yl	CH2	O	NH	C(Me)3	O
178	Ex 66	6-chloro-2-methyl-thiopyrimidin-4-yl	CH2	O	NH	C(Me)3	O
179	Ex 66	6(2,2-difluoroethoxy)-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
180	Ex 66	6(2,2,2-trifluoroethoxy) pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
181	Ex 66	6-difluoromethoxy-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
182	Ex 66	6-difluoromethoxy-2-methoxypyrimidin-4-yl	CH2	O	NH	C(Me)3	O
183	Ex 67	5-bromothiazol-2-yl	CH2	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
184	Ex 67	5-trifluoromethyl-thiazol-2-yl	CH2	O	NH	C(Me)3	O
185	Ex 67	5-iodothiazol-2-yl	CH2	O	NH	C(Me)3	O
186	Ex 67	5-chlorothiazol-2-yl	CH2	O	NH	C(Me)3	O
187	Ex 67	3-trifluoromethyl-isoxazol-5-yl	CH2	O	NH	C(Me)3	O
188	Ex 67	4-trifluoromethyl-oxazol-2-yl	CH2	O	NH	C(Me)3	O
189	Ex 67	2,2-difluoro-1,3-benzodioxol-5-yl	CH2	O	NH	C(Me)3	O
190	Ex 68	4-trifluoromethyl-pyridin-2-yl	CH2	NCH3	NH	C(Me)3	O
191	Ex 68	4-trifluoromethyl-pyridin-2-yl	CH2	NCH3		CH2C(Me)3	O
192	Ex 69	5-trifluoromethyl-thiazol-2-yl	CH2	NCH3	NH	C(Me)3	O
193	Ex 69	5-trifluoromethyl-thiazol-2-yl	CH2	NCH3		CH2C(Me)3	O
194	Ex 70	2,2-difluoro-1,3-benzodioxol-5-yl	CH2	NCH3	NH	C(Me)3	O
195	Ex 70	2,2-difluoro-1,3-benzodioxol-5-yl	CH2	NCH3		CH2C(Me)3	O
196	Ex 71	2-chlorothien-5-yl	CH2	O	NH	C(Me)3	
197	Ex 72	m-CF3 Ph	CH2	NH	NCH(Me)2	CH(Me)2	O
198		m-CF3 Ph	CH2	NH	NMe	C(Me)3	O
199		m-Br Ph	CH2	NCH2CH=CH2	-	CH2C(Me)2CH=CH2	O
200		m-Br Ph	CH2	NCH2CH=CH2	NH	C(Me)3	O
201		m-Br Ph	CH2	NCH2CH=CH2	-	CH2C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
202		m-OCF3 Ph	CH2	NH	NMe	C(Me)3	O
203		m-OCF3 Ph	CH2	NH	N-C(Me)3	Benzyl	O
204		m-CF3 Ph	CH2	NH	NH	CH(Me)2	O
205		3-Cl,4-F Ph	CH2	NH	-	CH2C(Me)3	O
206		3-Cl,4-F Ph	CH2	NH	NH	C(Me)3	O
207		3-Cl,4-F Ph	CH2	N-Me	NH	C(Me)3	O
208		3-Cl,4-F Ph	CH2	N-Me	-	CH2C(Me)3	O
209		3-Cl,4-F Ph	CH2	NCH2CH=CH2	NH	C(Me)3	O
210		3-Cl,4-F Ph	CH2	NCH2CH=CH2	-	CH2C(Me)3	O
211		3-Cl,4-F Ph	CH2	NH	-	CH2C(Me)2CH=CH2	O
212		3-Cl,4-F Ph	CH2	NMe	-	CH2C(Me)2CH=CH2	O
213		m-CF3 Ph	CH2	NEt	-	CHC(Me)3	O
214		m-CF3 Ph	CH2	NEt		CH2CH(Me)2Et	O
215		m-OCF3 Ph	CH2	NCHO		CH2C(Me)3	O
216		m-CF3 Ph	CH2	NCHO		CH2C(Me)3	O
217		m-CF3 Ph	CH2	NH	-	CH2C(Me)2Et	O
218		m-CF3 Ph	CH2	NMe	-	CH2C(Me)2Et	O
219		m-OCF3 Ph	CH2	NMe	-	CH2C(Me)2Et	O
220		m-Br Ph	CH2	S	NH	C(Me)2Et	O
221		m-Br Ph	CH2	NH	-	CH2C(Me)3	O
222		m-Br Ph	CH2	NH	-	CH2C(Me)2Et	O
223		m-Br Ph	CH2	NH	NH	C(Me)2Et	O
224		m-Br Ph	CH2	NMe	-	CH2C(Me)2CH=CH2	O
225		m-Br Ph	CH2	NH	-	CH2C(Me)2CH=CH2	O
226		m-CF3 Ph	CH2	NH	-	CH2C(Me)2CH=CH2	O
227		m-OCF3 Ph	CH2	NMe	-	CH2C(Me)2CH=CH2	O
228		m-Br Ph	CH2	NMe	-	CH2C(Me)3	O
229		m-Br Ph	CH2	NMe	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
230		m-Br Ph	CH2	NMe	-	CH2C(Me)2Et	O
231		m-Br Ph	CH2	NH	NH	C(Me)3	O
232		m-Br Ph	CH2	S	NH	C(Me)3	O
233		m-Br Ph	CH2	S	-	Me	O
234	ex 74	m-CF3 Ph	CH2	NEt	-	CH2NMe2	O
235	ex 75	m OCF3 Ph	CH2	NCH(OH)CO	N	C(Me)2CCH	O
236	ex 75	m-OCF3 Ph	CH2	NCH(OH)CO	N	C(Me)2CCH	O
237	ex 75	m-OCF3 Ph	CH2	CCOCH(OH)	N	C(Me)2CCH	O
238	ex 75	m-OCF3 Ph	CH2	CCOCH(OH)	N	C(Me)2CCH	O
239	ex 76	m-OCF3 Ph	O	CH2	NH	C(Me)2CCH	O
240	ex 16	m-OCF3 Ph	O	CH2	NH	C(Me)2Et	O
241	ex 27	m-CF3 Ph	CH2	NCH2-cyclopropyl	NH	C(Me)3	O
242	ex 27	m-CF3 Ph	CH2	NCH(Me)Et	NH	C(Me)3	O
243	ex 15	m-CF3,p-F Ph	O	CH2	O	C(Me)3	O
244	ex 77	m-CF3, p-F Ph	O	CH2	O	H	O
245	ex 77	m-CF3, p-F Ph	O	CH2	NH	C(Me)3	O
246	ex 77	m-CF3, p-F Ph	O	CH2	NH	C(Me)2CCH	O
247	ex 77	m-CF3, p-F Ph	O	CH2	NH	CH(Me)C(Me)3	O
248	ex 77	m-CF3, p-F Ph	O	CH2	NH	CH2C(Me)3	O
249	ex 77	m-CF3, p-F Ph	O	CH2	NH	1-Me-cyclobutyl	O
250	ex 76	m-CF3 Ph	O	CH2	O	CH2Ph	O
251	ex 76	m-CF3 Ph	O	CH2	O	H	O
252	ex 77	M-Cl, p-F Ph	O	CH2	NH	C(Me)3	O
253	ex 78	m-OCF3	CH2	NCH2CH2OCONHC(Me)3	NH	C(Me)3	O
254	ex 27	m-OCF3	CH2	NCH2CH2COOEt	NH	C(Me)3	O
255	ex 16	m-CF3, 4-F Ph	O	CH2	NH	C(Me)2Et	O
256	ex 76	m-OCF3 Ph	O	CH2	NH	1-Me-cyclopropyl	O
257	ex 76	m-OCF3 Ph	O	CH2	NH	CH2C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
258	15(THF)	m Cl, p-F Ph	O	CH2	O	C(Me)3	O
259	ex 96	m-CF3 Ph	O	CH2	NH	1-Me-cyclopentyl	O
260	ex 96	m-CF3 Ph	O	CH2	NH	1-Me-cyclobutyl	O
261	ex 96	m-CF3 Ph	O	CH2	NH	CH(Me)cyclopropyl	O
262	ex 94	m-CF3 Ph	O	NMe	-	CH2C(Me)3	O
263	ex 96	m-CF3 Ph	O	CH2	NH	1-Me-cyclohexyl	O
264	ex 96	m-CF3 Ph	O	CH2	NH	CH2C(Me)3	O
265	ex 93	m-CF3 Ph	O	NMe	NH	C(Me)3	O
266	ex 92	m-CF3 Ph	O	NCH2CH=CH2	-	CH2C(Me)3	O
267	ex 91	m-CF3 Ph	O	NCH2CH=CH2	NH	C(Me)3	O
268	ex 96	m-CF3 Ph	O	CH2	NH	1-Me-cyclopropyl	O
269	ex 92	m-OCF3 Ph	O	NMe	-	CH2C(Me)3	O
270	ex 95	m-CF3 Ph	O	NH	-	CH2C(Me)3	O
271	ex 92	m-OCF3 Ph	O	NH	-	CH2C(Me)3	O
272	ex 92	m-OCF3 Ph	O	NEt	-	CH2C(Me)3	O
273	ex 16	m-OCHF2 Ph	O	CH2	NH	C(Me)3	O
274	ex 16	m-OCHF2 Ph	O	CH2	NH	CH2C(Me)3	O
275	ex. 16	m-OCHF2 Ph	O	CH2	NH	C(Me)2Et	O
276	ex 16	m-OCHF2 Ph	O	CH2	NH	C(Me)2CH=CH2	O
277	ex 16	m-OCHF2 Ph	O	CH2	NH	C(Me)2CCH	O
278	ex 79	m-CF3 Ph	O	CH(Me)	O	CH2Ph	O
279	ex 79	m-CF3 Ph	O	CH(Me)	O	CH2Ph	O
280	ex 79	m-CF3 Ph	O	CH(Me)	NH	C(Me)3	O
281	ex 82	m-OCF3 Ph	CH2	NMe	NH	C(Me)2CF3	O
282	ex. 10	m-OCF3 Ph	CH2	NMe	-	CH2Si(Me)3	O
283	ex 80	m-CF3 Ph	CH2	NCH2C6H4OCF3-p	-	CH2C(Me)3	O
284	ex 81	m-CF3 Ph	CH2	NCH2C6H4OCF3-p	NH	C(Me)3	O
285	ex 80	m-CF3 Ph	CH2	NCH2-2-pyridyl	-	CH2C(Me)3	O
286	ex 81	m-CF3 Ph	CH2	NCH2-2-pyridyl	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
287	ex 80	m-CF3 Ph	CH2	NCH2-3-pyridyl	-	CH2C(Me)3	O
288	ex 81	m-CF3 Ph	CH2	NCH2-3-pyridyl	NH	C(Me)3	O
289	ex 80	m-CF3 Ph	CH2	NCH2-4-pyridyl	-	CH2C(Me)3	O
290	ex 81	m-CF3 Ph	CH2	NCH2-4-pyridyl	NH	C(Me)3	O
291	ex 83	m-CF3 Ph	S	NEt	-	CH2C(Me)3	O
292	ex 83	m-CF3 Ph	S	NEt	NH	C(Me)3	O
293	ex 83	m-CF3 Ph	S	NPr	-	CH2C(Me)3	O
294	ex 83	m-CF3 Ph	S	NPr	NH	C(Me)3	O
295	ex 83	m-CF3 Ph	S	NCH2CH=CH2	-	CH2C(Me)3	O
296	ex 83	m-CF3 Ph	S	NCH2CH=CH2	NH	C(Me)3	O
297		m-CF3 Ph	S	NCH2CCH	-	CH2C(Me)3	O
298		m-CF3 Ph	S	NCH2CCH	NH	C(Me)3	O
299	ex 84	m-CF3 Ph	S	NOMe	NH	C(Me)3	O
300	ex 83	m-CF3 Ph	S	NCH2CH=CH2	NH	CH2C(Me)3	O
301	ex 83	m-CF3 Ph	S	NCH2CCH	NH	CH2C(Me)3	O
302		m-CF3 Ph	S	NCH2CCH	NH	C(Me)2CH2Cl	O
303	ex 85	m-CF3 Ph	S	NCH2CO	N-	C(Me)3	O
304	ex 86	m-CF3 Ph	S	S	NH	C(Me)3	O
305	ex 5	m-OCF3	CH2	NH	-	CH=C(Me)2	O
306	ex 5	m-OCF3	CH2	NH	-	CH2C(Me)2	O
307	ex 5	m-OCF3	CH2	NH	-	CH2C(Me)2Et	O
308	ex 90	m-CF3	CH2	NMe	O	CH2CCl3	O
309	ex 20	m-OCHF2	CH2	S	NH	C(Me)3	O
310	ex 5	m-OCF3	CH2	NMe	-	CF2CF2CF3	O
311	ex 89	m-OCF3	CH2	NCH2CH2-	N-	C(Me)3	O
312	ex 27	m-OCF3	CH2	NCH2CH=CH2	NH	C(Me)3	O
313	ex 5	m-OCHF2	CH2	NH	-	CH2C(Me)3	O
314	ex 20	m-OCHF2	CH2	S	NH	C(Me)2CCH	O
315	ex 90	m-OCF3	CH2	NMe	O	C(Me)2CCl3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
316	ex 27	m-OCF3	CH2	NCH2CO2C(Me)3	NH	C(Me)3	O
317	ex 27	m-OCF3	CH2	NCH2COC(Me)3	NH	C(Me)3	O
318	ex 27	m-OCF3	CH2	NCH2CN	NH	C(Me)3	O
319	ex 20	m-OCF3	CH2	NMe	NH	CH2C(Me)3	O
320	ex 20	m-CF3	CH2	NCH2CH=CH2	NH	C(Me)3	O
321	ex 90	m-OCF3	CH2	NMe	O	CH2CCl3	O
322	ex 5	m-OCHF2	CH2	NEt	-	CH2C(Me)3	O
323	ex 20	m-OCHF2	CH2	NEt	NH	C(Me)3	O
324	ex 5	m-OCF3	CH2	NCH2CF3	-	CH2C(Me)3	O
325	ex 5	m-OCF3	CH2	NMe	-	CH2CH2CCl3	O
326	ex 88	m-OCF3	CH2	NMe	-	CF2CF3	O
327	ex 20	m-OCF3	CH2	NCH2CF3	NH	C(Me)3	O
328	ex 87	m-OCF3	CH2	NMe	-	CH2CH2CF3	O
329	ex 35	2-trifluoromethyl-benzoxazol-5-yl	S	O	NH	C(Me)3	O
330	ex 35	2-trifluoromethyl-benzoxazol-6-yl	S	O	NH	C(Me)3	O
331	ex 35	1,3-benzodioxol-5-yl	S	O	NH	C(Me)3	O
332	ex 62/67	5-methoxycarbonyl-thiazol-2-yl	CH2	O	NH	C(Me)3	O
333	ex 62/67	5-thiocyanato-thiazol-2-yl	CH2	O	NH	C(Me)3	O
334	ex 97	2,2-difluoro-1,3-benzodioxol-5-yl	CH2	NCH2CO	N	C(Me)3	O
335		6-trifluoromethoxy-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
336		6-methoxypyrimidin-4-yl	CH2	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
337		6-difluoromethyl-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
338		2,6-dimethoxy-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
339		2,6-bis(difluoromethoxy) pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
340		2 hydroxy-6-trifluoro methyl-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
341		2-hydroxy-6-difluoro methoxy-pyrimidin-4-yl	CH2	O	NH	C(Me)3	O
342		6-hydroxy-4-trifluoromethyl-pyridin-2-yl	CH2	O	NH	C(Me)3	O
343		6-hydroxy-4-difluoro methoxy-pyridin-2-yl	CH2	O	NH	C(Me)3	O
344		6-difluoromethoxy-pyrimidin-4-yl	CH2	O	NH	C(Me)2CF3	O
345		6-difluoromethoxy-pyrimidin-4-yl	CH2	O	NH	1-Me-cyclobutyl	O
346		4-trifluoromethyl-pyridin-2-yl	CH2	O	NH	C(Me)2CF3	O
347		4-trifluoromethyl-pyridin-2-yl	CH2	O	NH	1-Me-cyclobutyl	
348		5-methoxythiazol-2-yl	CH2	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
349		5 methoxythiazol 2-yl	CH2	O	NH	1-Me-cyclobutyl	
350		5-trifluoromethyl-1,2,4-oxadiazol-2-yl	CH2	O	NH	C(Me)3	O
351		5-trifluoromethyl isoxazol-3-yl	CH2	O	NH	C(Me)3	O
352		5-trifluoromethyl isoxazol-3-yl	CH2	O	NH	C(Me)2CF3	O
353		5-trifluoromethyl oxazol-2-yl	CH2	O	NH	C(Me)3	O
354		1-methyl-5-trifluoro-methylpyrazol-3-yl	CH2	O	NH	C(Me)3	O
355		1-methyl-3-trifluoro-methylpyrazol-5-yl	CH2	O	NH	C(Me)3	O
356		2-trifluoromethyl-pyridin-4-yl N oxide	CH2	O	NH	C(Me)3	O
357		2-chloropyridin-4-yl N-oxide	CH2	O	NH	C(Me)3	O
358		1 methyl-2-trifluoromethylpyrid-5-inium iodide	CH2	O	NH	C(Me)3	O
359		1,2,4-triazol-4-yl	CH2	O	NH	C(Me)3	O
360		2,2-difluorobenzo-dioxol 4-yl	CH2	O	NH	C(Me)3	O
361		4-trifluoromethyl imidazol-1-yl	CH2	O	NH	C(Me)3	O
362		4-difluoromethoxy imidazol-1-yl	CH2	O	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
363		3-trifluoromethyl isothiazol-5-yl	CH2	O	NH	C(Me)3	O
364		5-trifluoromethyl isothiazol-3-yl	CH2	O	NH	C(Me)3	O
365		3-trifluoromethyl-pyridazin-5-yl	CH2	O	NH	C(Me)3	O
366		5-trifluoromethyl-pyridazin-3-yl	CH2	O	NH	C(Me)3	O
367		4-difluoromethoxy-pyridin-2-yl	CH2	O	NH	C(Me)3	O
368		2-difluoromethoxy-pyridin-4-yl	CH2	O	NH	C(Me)3	O
369		5-trifluoromethyl-1,2,4-triazol-3-yl	CH2	O	NH	C(Me)3	O
370		1-methyl-3-trifluoromethyl-1,2,4-triazol-5-yl	CH2	O	NH	C(Me)3	O
371		4-trifluoromethyl-pyridin-2-yl	CH2	NCH2CO	N	C(Me)3	O
372		5-trifluoromethyl-thiazol-2-yl	CH2	NCH2CO	N	C(Me)3	O
373		2-trifluoromethyl-pyridin-4-yl	CH2	NCH2CO	N	C(Me)3	O
374		5-trifluoromethyl-isoxazol-3-yl	CH2	NCH2CO	N	C(Me)3	O
375		6-trifluoromethyl-pyrimidin-4-yl	CH2	NCH2CO	N	C(Me)3	O
376		6-difluoromethoxy-pyrimidin-4-yl	CH2	NCH2CO	N	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
377		5-bromothiazol-2-yl	CH2	NCH2CO	N-	C(Me)3	O
378		2-methoxy-6-difluoromethoxy pyrimidin-4-yl	CH2	NCH2CO	H	C(Me)3	O
379		2,6-bis(difluoromethoxy) pyrimidin-4-yl	CH2	NCH2CO	H	C(Me)3	O
380		5-trifluoromethyl-oxazol-2-yl	CH2	NCH2CO	H	C(Me)3	O
381		2,2-difluorobenzo-dioxol 5-yl	O	O	NH	C(Me)3	O
382		2,2-difluorobenzo-dioxol 5-yl	O	CH2	NH	C(Me)3	O
383		2,2-difluorobenzo-dioxol 5-yl	O	CH(Me)	NH	C(Me)3	O
384		2,2-difluorobenzo-dioxol 5-yl	O	N-Me	NH	C(Me)3	O
385		2,2 difluorobenzo-dioxol 5-yl	O	N-Et	NH	C(Me)3	O
386		2,2 difluorobenzo-dioxol 5-yl	O	N-Me		CH2C(Me)3	O
387		2,2-difluorobenzo-dioxol 5-yl	O	O	NH	C(Me)2CCH	O
388		2,2-difluorobenzo-dioxol 5-yl	O	NCH2CO	H	C(Me)3	O
389		4-trifluoromethyl-pyridin-2-yl	O	O	NH	C(Me)3	O
390		2-trifluoromethyl-pyridin-4-yl	O	CH2	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
391		6-difluoromethoxy pyrimidin-4-yl	O	O	nil	C(Me)3	O
392		6-trifluoromethyl-pyrimidin-4-yl	O	O	nil	C(Me)3	O
393		5-trifluoromethyl-thiazol-2-yl	O	O	nil	C(Me)3	O
394		5-trifluoromethyl-thiazol-2-yl	O	CH2	nil	C(Me)3	O
395		5-trifluoromethyl-thiazol-2-yl	O	N Me		CH2C(Me)3	O
396		5-trifluoromethyl-thiazol-2-yl	O	N-Et		CH2C(Me)3	O
397		5 trifluoromethyl-oxazol-2-yl	O	O	nil	C(Me)3	O
398		5-trifluoromethyl-isoxazol-3-yl	O	O	nil	C(Me)3	O
399		3-trifluoromethyl-isoxazol-5-yl	O	O	nil	C(Me)3	O
400		2,6-bis(difluoromethoxy) pyrimidin-4-yl	CH2	N-Me		CH2C(Me)3	O
401		6-difluoromethoxy-2-methoxy-pyrimidin-4-yl	CH2	N-Et		CH2C(Me)3	O
402		6-difluoromethoxy-pyrimidin-4-yl	CH2	N-Me	nil	C(Me)3	O
403		6 difluoromethoxy-pyrimidin-4-yl	CH2	NH	nil	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
404		6-difluoromethoxy 2-hydroxypyrimidin-4-yl	CH2	N-Me	NH	C(Me)2CCH	O
405		5 trifluoromethyl-oxazol-2-yl	CH2	N-Me	NH	C(Me)3	O
406		5-trifluoromethyl-oxazol-2-yl	CH2	N-Me	-	CH2C(Me)3	O
407		5-trifluoromethyl-thiazol-2-yl	CH2	N-Et		CH2C(Me)3	O
408		5-trifluoromethyl-thiazol-2-yl	CH2	N-Et	NH	C(Me)2CCH	O
409		5-trifluoromethyl-thiazol-2-yl	CH2	N-Et	NH	C(Me)2CH-CH2	O
410		4-trifluoromethyl-pyridin-2-yl	CH2	N-Et	-	CH2C(Me)2CCH	O
411		2,2-difluoro-benzodioxol 4-yl	CH2	N-Et	NH	1 Me cyclobutyl	O
412		5 bromothiazol-2-yl	CH2	N-Me	-	CH2C(Me)2CF3	O
413		2-chlorothien-4-yl	CH2	N-Me	-	CH2C(Me)3	O
414		2-chlorothien-4-yl	CH2	N-Me	NH	C(Me)3	O
415		2-chlorothien-4-yl	CH2	CH2	NH	C(Me)3	O
416		2-chlorothien-4-yl	S	O	NH	C(Me)3	O
417		2-chlorothien-4-yl	O	O	NH	C(Me)3	O
418		2-chlorothien-4-yl	O	CH2	NH	C(Me)3	O
419		2-trifluoromethyl-thien-4-yl	CH2	N-Me		CH2C(Me)3	O
420		2-trifluoromethyl-thien-4-yl	CH2	N-Me	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
421		2-trifluoromethyl-thien-4-yl	CH2	CH2	NH	C(Me)3	O
422		2-trifluoromethyl-thien-4-yl	S	O	NH	C(Me)3	O
423		2-trifluoromethyl-thien-4-yl	CH2	O	NH	C(Me)3	O
424		2-trifluoromethyl-thien-4-yl	O	O	NH	C(Me)3	O
425		2-trifluoromethyl-thien-4-yl	O	CH2	NH	C(Me)3	O
426		2-trifluoromethoxy-thien-4-yl	CH2	N-Me		CH2C(Me)3	O
427		2-trifluoromethoxy-thien-4-yl	CH2	N-Me	NH	C(Me)3	O
428		2-trifluoromethoxy-thien-4-yl	CH2	O	NH	C(Me)3	O
429		2-trifluoromethoxy-thien-4-yl	O	O	NH	C(Me)3	O
430		4-chlorothien-2-yl	CH2	NH		CH2C(Me)3	O
431		4-chlorothien-2-yl	CH2	N-Me	NH	C(Me)3	O
432		4-chlorothien-2-yl	CH2	CH2	NH	C(Me)3	O
433		4-chlorothien-2-yl	O	O	NH	C(Me)3	O
434		4-chlorothien-2-yl	O	CH2	NH	C(Me)3	O
435		4-chlorothien-2-yl	S	O	NH	C(Me)3	O
436		4-trifluoromethyl-thien-2-yl	CH2	NH		CH2C(Me)3	O
437		4-trifluoromethyl-thien-2-yl	CH2	N-Me	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
438		4-trifluoromethyl-thien-2-yl	CH2	CH2	NH	C(Me)3	O
439		4-trifluoromethyl-thien-2-yl	O	O	NH	C(Me)3	O
440		4-trifluoromethyl-thien-2-yl	O	CH2	NH	C(Me)3	O
441		4-trifluoromethyl-thien-2-yl	S	O	NH	C(Me)3	O
442		4-trifluoromethoxy-thien-2-yl	CH2	O	NH	C(Me)3	O
443		4-trifluoromethoxy-thien-2-yl	CH2	N-Me	NH	C(Me)3	O
444		4-trifluoromethoxy-thien-2-yl	CH2	NH		CH2C(Me)3	O
445		4-trifluoromethoxy-thien-2-yl	O	O	NH	C(Me)3	O
446		2-chlorothien-5-yl	CH2	NH	-	CH2C(Me)3	O
447		2-chlorothien-5-yl	CH2	N-Me	NH	C(Me)3	O
448		2-chlorothien-5-yl	CH2	CH2	NH	C(Me)3	O
449		2-chlorothien-5-yl	O	O	NH	C(Me)3	O
450		2-chlorothien-5-yl	O	CH2	NH	C(Me)3	O
451		2-chlorothien-5-yl	S	O	NH	C(Me)3	O
452		2-trifluoromethyl-thien-5-yl	CH2	NH		CH2C(Me)3	O
453		2-trifluoromethyl-thien-5-yl	CH2	N-Me	NH	C(Me)3	O
454		2-trifluoromethyl-thien-5-yl	CH2	CH2	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
455		2-trifluoromethyl-thien-5-yl	O	O	NH	C(Me)3	O
456		2-trifluoromethyl-thien-5-yl	O	CH2	NH	C(Me)3	O
457		2-trifluoromethyl-thien-5-yl	S	O	NH	C(Me)3	O
458		2-trifluoromethoxy-thien-5-yl	CH2	O	NH	C(Me)3	O
459		2-trifluoromethoxy-thien-5-yl	CH2	N-Me	NH	C(Me)3	O
460		2-trifluoromethoxy-thien-5-yl	CH2	NH		CH2C(Me)3	O
461		2-trifluoromethoxy-thien-5-yl	O	O	NH	C(Me)3	O
462		2-trifluoromethyl-fur-5-yl	CH2	NH		CH2C(Me)3	O
463		2-trifluoromethyl-fur-5-yl	CH2	N-Me	NH	C(Me)3	O
464		2-trifluoromethyl-fur-5-yl	CH2	CH2	NH	C(Me)3	O
465		2-trifluoromethyl-fur-5-yl	O	O	NH	C(Me)3	O
466		2-trifluoromethyl-fur-5-yl	O	CH2	NH	C(Me)3	O
467		2-trifluoromethyl-fur-5-yl	S	O	NH	C(Me)3	O
468		2-trifluoromethyl-fur-4-yl	CH2	NH		CH2C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
469		2-trifluoromethyl-fur-4-yl	CH2	N-Me	HH	C(Me)3	O
470		2-trifluoromethyl-fur-4-yl	CH2	CH2	HH	C(Me)3	O
471		2-trifluoromethyl-fur-4-yl	O	O	HH	C(Me)3	O
472		2-trifluoromethyl-fur-4-yl	O	CH2	HH	C(Me)3	O
473		2-trifluoromethyl-fur-4-yl	S	O	HH	C(Me)3	O
474		4-trifluoromethyl-fur-2-yl	CH2	NH		CH2C(Me)3	O
475		4-trifluoromethyl-fur-2-yl	CH2	N-Me	HH	C(Me)3	O
476		4-trifluoromethyl-fur-2-yl	CH2	CH2	HH	C(Me)3	O
477		4-trifluoromethyl-fur-2-yl	O	O	HH	C(Me)3	O
478		4-trifluoromethyl-fur-2-yl	O	CH2	HH	C(Me)3	O
479		4-trifluoromethyl-fur-2-yl	S	O	HH	C(Me)3	O
480		2-trifluoromethyl-1-methylpyrrol-4-yl	CH2	NH		CH2C(Me)3	O
481		2-trifluoromethyl-1-methylpyrrol-4-yl	CH2	N-Me	HH	C(Me)3	O
482		2-trifluoromethyl-1-methylpyrrol-4-yl	CH2	CH2	HH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
483		2-trifluoromethyl-1-methylpyrrol-4-yl	O	O	NH	C(Me)3	O
484		2-trifluoromethyl-1-methylpyrrol-4-yl	O	CH2	NH	C(Me)3	O
485		2-trifluoromethyl-1-methylpyrrol-4-yl	S	O	NH	C(Me)3	O
486		2-trifluoromethyl-1-methylpyrrol-5-yl	CH2	NH		CH2C(Me)3	O
487		2-trifluoromethyl-1-methylpyrrol-5-yl	CH2	N-Me	NH	C(Me)3	O
488		2-trifluoromethyl-1-methylpyrrol-5-yl	CH2	CH2	NH	C(Me)3	O
489		2-trifluoromethyl-1-methylpyrrol-5-yl	O	O	NH	C(Me)3	O
490		2-trifluoromethyl-1-methylpyrrol-5-yl	O	CH2	NH	C(Me)3	O
491		2-trifluoromethyl-1-methylpyrrol-5-yl	S	O	NH	C(Me)3	O
492		3-trifluoromethyl-1-methylpyrrol-5-yl	CH2	NH		CH2C(Me)3	O
493		3-trifluoromethyl-1-methylpyrrol-5-yl	CH2	N-Me	NH	C(Me)3	O
494		3-trifluoromethyl-1-methylpyrrol-5-yl	CH2	CH2	NH	C(Me)3	O
495		3-trifluoromethyl-1-methylpyrrol-5-yl	O	O	NH	C(Me)3	O
496		3-trifluoromethyl-1-methylpyrrol-5-yl	O	CH2	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
497		3 trifluoromethyl 1-methylpyrrol-5-yl	S	O	NH	C(Me)3	O
498		3-(pentafluoroethyl)-phenyl	CH2	NH		CH2C(Me)3	O
499		3 (pentafluoroethyl)-phenyl	CH2	N-Me	NH	C(Me)3	O
500		3 (pentafluoroethyl)-phenyl	CH2	CH2	NH	C(Me)3	O
501		3-(pentafluoroethyl)-phenyl	O	O	NH	C(Me)3	O
502		3-(pentafluoroethyl)-phenyl	O	CH2	NH	C(Me)3	O
503		3-(pentafluoroethyl)-phenyl	S	O	NH	C(Me)3	O
504		1 methylpyrid 3-inium iodide	CH2	O	NH	C(Me)3	O
505		3-CN Ph	CH2	N-Me	NH	C(Me)3	O
506		3-CF3, 4-CN Ph	CH2	N-Et	NH	C(Me)2Et	O
507		3-CF3, 5-CN Ph	CH2	N-Pr	NH	C(Me)3	O
508		3-CF3, 6-CN	CH2	N-Et	NH	C(Me)2CCH	O
509		3-SO2NH2 Ph	CH2	N-Me	NH	C(Me)2CH=CH2	O
510		3-SO2F Ph	CH2	N-Me	NH	1 Me-cyclobutyl	O
511		3-SO2F Ph	CH2	N-Me	NH	C(Me)3	O
512		3-SO2N3 Ph	CH2	N-Et	NH	C(Me)2CH2Cl	O
513		3-OCF2CN Ph	CH2	N-allyl	NH	C(Me)3	O
514		3-trifluoromethyl-benzisoxazol-5-yl	CH2	N-Et	NH	C(Me)2Et	O
515		benzisoxazol-5-yl	CH2	N-Me	NH	C(Me)3	O
516		3-OCF3 Ph	CH2	N-OEt	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
517		3-OCHF2 Ph	CH2	N-Opr	NH	C(Me)3	O
518		3-CF3 Ph	CH2	N-OBn	NH	C(Me)2Et	O
519		3-OCF3 Ph	CH2	N-OEt	NH	C(Me)2CCH	O
520		3-OCF3 Ph	CH2	CH2CCCl	NH	C(Me)3	O
521		3-CF3 Ph	CH2	(CH2)2F	NH	C(Me)3	O
522		3-OCF3 Ph	CH2	N-Me	NH	C(Me)2OMe	O
523		3-OCHF2 Ph	CH2	N-Et	NH	C(Me)2OMe	O
524		3-OCF3 Ph	CH2	N-Et	NH	C(Me)2CN	O
525		3-OCHF2 Ph	CH2	N-Me	NH	C(Me)2CN	O
526		3-CF3 Ph	CH2	N-Me	NH	C(Me)2H	O
527		3-OCF3 Ph	CH2	N-Et	NH	C(Me)2H	O
528		3-OCHF2 Ph	CH2	N-OMe	NH	C(Me)2H	O
529		3-CN Ph	CH2	N-Et		CH2C(Me)3	O
530		3-CF3, 4-CN Ph	CH2	N-Me		CH2C(Me)3	O
531		3-CF3, 5-CN Ph	CH2	N-Et		CH2C(Me)3	O
532		3-CF3, 6-CN Ph	CH2	N-Pr		CH2C(Me)2H	O
533		3-SO2NH2 Ph	CH2	N-Et		CH2C(Me)3	O
534		3-SO2F Ph	CH2	N-Et		CH2C(Me)3	O
535		3-OCHF2 Ph	O	N-Me	NH	C(Me)3	O
536		3-OCF3 Ph	O	N-Et	NH	C(Me)2Et	O
537		3-CF3 Ph	O	N-Pr	NH	C(Me)3	O
538		3-OCF3 Ph	O	N-Et	NH	C(Me)2CCH	O
539		3-OCF3 Ph	O	N-Me	NH	C(Me)2CH=CH2	O
540		3-OCHF2 Ph	O	N-Me	NH	1-Me-cyclobutyl	O
541		3-OCF3 Ph	O	N-Me	NH	C(Me)3	O
542		3-OCF3 Ph	O	N-Et	NH	C(Me)3	O
543		3-OCHF2 Ph	O	N-allyl	NH	C(Me)3	O
544		3-CF3, 4-F Ph	O	N-Me	NH	C(Me)3	O
545		3-CF3, 4-F Ph	O	N-Et	NH	C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
546		3 CF3, 4 F Ph	O	N Et	NH	1 Me cyclobutyl	O
547		3-CF3, 4-F Ph	O	N-Pr	NH	C(Me)3	O
548		3-Cl, 4-F Ph	O	N-Me	NH	C(Me)3	O
549		3 Cl, 4 F Ph	O	N-Et	NH	1 Me cyclobutyl	O
550		3-Cl, 4-F Ph	O	N-Et	NH	C(Me)3	O
551		3-Cl, 4-F Ph	O	N-Pr	NH	C(Me)3	O
552		3-OCHF2 Ph	O	N-Me	-	CH2C(Me)3	O
553		3-OCHF2 Ph	O	N-Et	-	CH2C(Me)3	O
554		3 OCHF2 Ph	O	N-Et	-	CH2C(Me)2H	O
555		3-OCHF2 Ph	O	N-Pr	-	CH2C(Me)3	O
556		3-CF3, 4-F Ph	O	N-Me		CH2C(Me)3	O
557		3-CF3, 4-F Ph	O	N-Et		CH2C(Me)3	O
558		3 CF3, 4-F Ph	O	N-Et		CH2C(Me)2H	O
559		3-CF3, 4-F Ph	O	N-Pr		CH2C(Me)3	O
560		3-Cl, 4-F Ph	O	N-Me	-	CH2C(Me)3	O
561		3-Cl, 4-F Ph	O	N-Et	-	CH2C(Me)3	O
562		3-Cl, 4-F Ph	O	N-Et	-	CH2C(Me)2H	O
563		3-Cl, 4-F Ph	O	N-Pr		CH2C(Me)3	O
564		3-CF3 Ph	O	CH2	NH	C(Me)2CCH	O
565		3-OCHF2 Ph	O	CH2	NH	C(Me)2CCH	O
566		3-CF3, 4-F Ph	O	CH2	NH	C(Me)2CCH	O
567		3-Cl, 4 F Ph	O	CH2	NH	C(Me)2CCH	O
568		3-Cl Ph	O	CH2	NH	C(Me)2CCH	O
569		3,5-Cl2 Ph	O	CH2	NH	C(Me)2CCH	O
570		3-CF3 Ph	O	CH2	NH	C(Me)2CHCH2	O
571		3-OCHF2 Ph	O	CH2	NH	C(Me)2CHCH2	O
572		3-CF3, 4-F Ph	O	CH2	NH	C(Me)2CHCH2	O
573		3-Cl, 4-F Ph	O	CH2	NH	C(Me)2CHCH2	O
574		3-Cl Ph	O	CH2	NH	C(Me)2CHCH2	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
575		3,5-Cl2 Ph	O	CH2	NH	C(Me)2CHCH2	O
576		3-CF3 Ph	O	CH2	NH	C(Me)2H	O
577		3-OCHF2 Ph	O	CH2	NH	C(Me)2CN	O
578		3-Cl Ph	O	CH2	NH	1-Me-cyclopropyl	O
579		3-CF3 Ph	O	CH2	NH	C(Me)2CH2Cl	O
580		3-OCF3 Ph	O	CH2	NH	C(Me)2H	O
581		3-OCF3 Ph	O	CH2	NH	C(Me)2CN	O
582		3-OCF3, 4-F Ph	CH2	NMe	NH	C(Me)3	O
583		3-OCF3, 4-F Ph	CH2	NMe	-	CH2C(Me)3	O
584		3-OCF3, 4-F Ph	CH2	NEt	-	CH2C(Me)3	O
585		3-OCF3, 4-F Ph	CH2	NMe	NH	C(Me)3	O
586		3-OCF3, 4-F Ph	CH2	NMe	-	CH2C(Me)3	O
587		3-OCF3, 4-F Ph	CH2	NEt	-	CH2C(Me)3	O
588		3-OMe, 4-F Ph	CH2	NMe	NH	C(Me)3	O
589		3-OMe, 4-F Ph	CH2	NMe	-	CH2C(Me)3	O
590		3-OMe, 4-F Ph	CH2	NEt	-	CH2C(Me)3	O
591		3-OMe, 4-Cl Ph	CH2	NMe	NH	C(Me)3	O
592		3-OMe, 4-Cl Ph	CH2	NMe	-	C(Me)3	O
593		3-OCF3 Ph	CH2	NMe		CF2C(Me)3	O
594		3-OCF3 Ph	CH2	NH	-	CF2C(Me)3	O
595		3-OCF3 Ph	CH2	NCH2CH=CH2	-	CF2C(Me)3	O
596		3-OCF3 Ph	CH2	NMe	-	CH2CF(Me)2	O
597		3-OCF3 Ph	CH2	NMe	-	CH2CCl(Me)2	O
598		3-OCF3 Ph	CH2	NMe	-	CH2C(OH)(Me)2	O
599		3-OCF3 Ph	CH2	NMe	-	CH2C(OMe)(Me)2	O
600		3-OCF3 Ph	CH2	NMe	-	CH2C(OH)(CF3)2	O
601		3-OCF3 Ph	CH2	NMe	-	CH2CCl3	O
602		3-OCF3 Ph	CH2	NH	-	CH2CCl3	O
603		3-OCF3 Ph	CH2	NCH2CH=CH2	-	CH2CCl3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
604		3-OCF3 Ph	CH2	NEt	-	CH2CCl3	O
605		3-OCF3 Ph	CH2	NMe	NH	CH2CCl3	O
606		3-OCF3 Ph	CH2	NCH2CH2CH2-	N-	C(Me)3	O
607		3-OCF3 Ph	CH2	NCH2CH2CO-	N-	C(Me)3	O
608		3-OCF3 Ph	CH2	NMe	-	CH2cyclopropyl	O
609		3-OCF3 Ph	CH2	NMe	-	CH2cyclobutyl	O
610		3-OCF3 Ph	CH2	NMe	-	CH2cyclopentyl	O
611		3-OCF3 Ph	CH2	NMe		CH2-1-methylcyclopropyl	O
612		3-OCF3 Ph	CH2	NMe		CH2-1-methylcyclobutyl	O
613		3-OCF3 Ph	CH2	NMe		CH2-1-methylcyclopentyl	O
614		3CF3 4Me Ph	CH2	NH	NH	tBu	O
615		3CF3 4Me Ph	CH2	NMe	NH	C(Me)2Et	O
616		3CF3 4Me Ph	CH2	N-Allyl	NH	C(Me)2CH=CH2	O
617		3CF3 4Me Ph	S	NMe	NH	tBu	O
618		3CF3 4Me Ph	O	NEt	-	CH2C(Me)3	O
619		3Br 4F Ph	CH2	NEt	NH	tBu	O
620		3Br 4F Ph	CH2	N-Allyl	NH	C(Me)2Et	O
621		3Br 4F Ph	CH2	NMe	NH	C(Me)2CH=CH2	O
622		3Br 4F Ph	S	NEt	NH	tBu	O
623		3Br 4F Ph	CH2	NMe	-	CH2C(Me)2Et	O
624		3,4,5 triF Ph	CH2	N-Allyl	NH	tBu	O
625		3,4,5 triF Ph	CH2	NMe	NH	C(Me)2Et	O
626		3,4,5 triF Ph	CH2	NEt	NH	C(Me)2CH=CH2	O
627		3,4,5 triF Ph	S	NH	NH	C(Me)2CH=CH2	O
628		3,4,5 triF Ph	CH2	NMe	-	CH2C(Me)3	O
629		3,4,5 triF Ph	CH2	N-Allyl	-	CH2C(Me)3	O

Comp	Prep.	A	X	Y	(Z)n	R1	W
630		3-CHF2 Ph	CH2	NMe	NH	1 Me cyclopropyl	O
631		3-CHF2 Ph	CH2	NEt	NH	1-Me-cyclobutyl	O
632		3-CHF2 Ph	O	NEt	NH	1-CCH- cyclopropyl	O
633		3-CHF2 Ph	O	NMe	NH	1-CN- cyclopentyl	O
634		3 CHF2 Ph	CH2	NPr	NH	1 CN cyclohexyl	O
635		3-CF2Cl Ph	CH2	NEt	NH	1 Me cyclohexyl	O
636		3-CF2Cl Ph	O	NMe	NH	C(Et)3	O
637		3-OCF3 Ph	CH2	NMe	S	C(Me)3	O
638		3-OCF3 Ph	CH2	NEt	S	CH2C(Me)3	O
639		3-CF3 Ph	O	NMe	S	C(Et)2Me	O
640		3-OCF3 Ph	CH2	NOEt	NH	C(Me)3	O
641		3-CF3 Ph	CH2	NOPr	NH	C(Me)3	O
642		4-chlorothien-2-yl	CH2	O	NH	C(Me)3	O
643		2-trifluoromethyl-thien-2-yl	CH2	O	NH	C(Me)3	O
644		2-trifluoromethyl-fur-5-yl	CH2	O	NH	C(Me)3	O
645		2-trifluoromethyl-fur-4-yl	CH2	O	NH	C(Me)3	O
646		4 trifluoromethyl-fur-2-yl	CH2	O	NH	C(Me)3	O
647		2-trifluoromethyl-1-methylpyrrol-4-yl	CH2	O	NH	C(Me)3	O
648		2-trifluoromethyl-1-methylpyrrol-5-yl	CH2	O	NH	C(Me)3	O
649		3-trifluoromethyl-1-methylpyrrol-5-yl	CH2	O	NH	C(Me)3	O

Compounds of formula I are suitably prepared by a variety of processes and some of these are discussed below.

For example, compounds of General formula I may be synthesised from compounds of general formula II, wherein A, R^2, R^3 and X are as defined for General formula I and R^{15} is OH, SH or NHR^6, wherein R^6 is as defined for General formula I. Compounds of general formula II in which R^{15} is OH, SH and NHR^6 give rise to compounds of general formula I in which Y is O, S and NR^6 respectively.

Reaction of a compound of general formula II with compounds of general formula R^1COCl, R^1OCOCl, R^1-N=C=O and R^1R^4NCOCl gives rise to compounds of general formula I in which W is O and n is 0, Z is O, Z is NH and Z is NR^4 respectively.

Compounds of general formula I in which W is S and Z is NH may be prepared by the reaction of a compound of general formula II with a compound of general formula R^1-N=C=S.

Compounds of general formula II in which R^{15} is OH or NR^6 may also be converted to compounds of general formula I in which both Y and W are O by reaction with a compound of general formula $R^1O(C=O)O(C=O)OR^1$.

The conversion of a compound of general formula II to a compound of general formula I may be carried out in an organic solvent such as chloroform, dichloromethane or toluene at a temperature of from 0 to 50°C, preferably at room temperature. The reaction generally proceeds most favourably in the presence of a base which may be an amine such as 4-N,N dimethylaminopyridine (DMAP) or triethylamine. Alternatively, when the compound of general formula II is reacted with an isocyanate, the base may be replaced with a catalytic amount of boron trifluoride etherate.

Compounds of general formula I where X is CR^4R^5, Z is NR^4, W is O, Y is NR^6 and n is 1 may be prepared by treatment of a compound of general formula II where R^{15} is NHR^6 with a carbamoyl chloride of general formula R^1R^4NCOCl in a suitable solvent such as N,N-dimethyl formamide (DMF) in the presence of a suitable base such as DMAP at an appropriate temperature between 0°C and 100°C, usually at room temperature. Compounds of the formula R^1R^4NCOCl are known in the art or may be prepared by the treatment of an amine of formula NHR^1R^4 with phosgene in a suitable solvent such as toluene.

Compounds of general formula II may be synthesised by various routes

from compounds of general formula III, wherein A, R^2, R^3 and X are as defined for general formula I and R^{20} is a leaving group such as Cl, Br, I, methane sulphonyloxy or toluene sulphonyloxy.

Compounds of general formula II in which R^{15} is NHR^6 and R^6 is H may be prepared from compounds of general formula III by reaction with an alkali metal azide such as sodium azide to give the equivalent azide compound followed by reduction of the azide by any known method, for example using 1,3-propane dithiol in a basic solvent, to give the appropriate compound of general formula II. The first step of the reaction may be carried out at a temperature of from 0 to 30°C, but preferably at room temperature in a solvent such as dimethylformamide (DMF). The conversion of the azide to a compound of general formula II is preferably carried out under an inert atmosphere such as nitrogen at 0 to 30°C, most suitably at room temperature. The solvent may be an amine such as triethylamine.

Compounds of general formula II in which R^{15} is NHR^6 and R^6 is other than hydrogen may be prepared from compounds of general formula III by reaction with a compound of formula NH_2R^6, wherein R^6 is as defined in general formula I. The reaction may be carried out at a temperature of from 0 to 80°C, preferably from 0°C to room temperature and it is particularly preferred for the reaction to be initiated at 0°C and subsequently allowed to warm to room temperature after most of the reactant has been converted to product. The reaction is generally carried out in an organic solvent, particularly an ether such as tetrahydrofuran (THF).

Compounds of general formula II in which R^{15} is OH may be prepared from compounds of general formula III, in which R^{20} is Cl, by reaction with an aqueous base, typically a weak base such as an alkali metal bicarbonate. In some cases, however, particularly when the group A is a heterocyclic group, it is preferable to use mildly acidic conditions which may be provided by, for example, aqueous potassium hydrogen phosphate. Typically, a solution of the compound of general formula III in a solvent such as an ether, for example THF, is stirred with the aqueous reagent at a temperature of from 0° to 50°C, but preferably at room temperature.

Compounds of general formula II in which R^{15} is OH may also be prepared from compounds of general formula IV, wherein A, R^2, R^3 and X are as defined in general formula I, by reaction with a strong base such as

$LiN(Si(CH_3)_3)_2$ or $LiN(CH(CH_3)_2)_2$ followed by reaction with a compound possessing an active oxygen, such as a compound of formula V in which, for example, Ar is a p-tolyl group and Ar' is a phenyl group. The reaction is suitably effected in a solvent such as THF at a temperature of from about -100^o to 30^oC, preferably from -80^o to 0^oC.

A method for the preparation of compounds of general formula II in which R^{15} is OH and X is CH_2 is by the reaction of a derivative of general formula VI in which A is as defined for general formula I with a compound of general formula VII wherein R^2 and R^3 are as defined for general formula I, but are preferably hydrogen and R^4 and R^5 are hydrogen. The reaction may be conducted in the absence of a solvent and at a temperature of from about 100^o to 300^o, preferably about 150^o. This reaction is novel and forms a further aspect of the invention.

The reaction works particularly well for compounds in which A is phenyl or substituted phenyl.

Compounds of general formulae VI and VII are, in general, readily available or may be prepared by methods known to those skilled in the art. Some examples of the synthesis of compounds of general formula VI are given in the examples below. Compounds of general formula V may be prepared as described in J. Org. Chem., (1988) 53, 2087.

Compounds of general formula III in which R^{20} is Cl or Br may be prepared from compounds of general formula IV as defined above by chlorination or bromination as appropriate. The particular method of halogenation will depend upon the nature of the groups A and X but an appropriate route may be determined by the skilled chemist. For example, when X is S, chlorination may be carried out using an agent such as sulphuryl chloride, N-chlorosuccinimide or chlorine. The reaction may take place in a chlorinated solvent such as dichloromethane. The chlorination reaction will preferably be carried out at a temperature of -15^o to 5^oC, preferably -5^o to 0^oC. When X is CH_2, bromination is typically carried out by reaction with bromine in the presence of phosphorus tribromide or with N-bromosuccinimide in a halogenated solvent. The reaction will often be conducted at a temperature of from about 70^o to 150^oC and in these circumstances it will be necessary to use a high boiling solvent such as chlorobenzene. An inert atmosphere such as nitrogen will generally be employed.

Compounds of general formula II in which R^{15} is OH and X is CH_2 may be converted to compounds of general formula III in which R^{20} is Cl and X is CH_2 by treatment with a chlorinating agent, particularly thionyl chloride. The reaction may be initiated at room temperature and maintained at room temperature for about 2 to 14 hours before heating, preferably to the reflux temperature of the solvent.

Compounds of general formula III in which R^{20} is Br and X is CH_2 may also be prepared from compounds of general formula II in which R^{15} is OH and X is CH_2. In this case, the compound of general formula II may be treated with agents such as 1,2-dibromotetrachloroethane and triphenylphosphine. The solvent employed will preferably be an ether, particularly diethyl ether and the reaction may be initiated at a temperature from about -10^{o} to $5^{o}C$, preferably about $0^{o}C$ and subsequently allowed to warm to room temperature.

Compounds of general formula III wherein R^{20} is methane sulphonyloxy or toluene sulphonyloxy may be synthesised from compounds of general formula II wherein R^{15} is OH by reaction with methane sulphonyl chloride or toluene sulphonyl chloride as appropriate. The reaction may be conducted at a temperature of from 0^{o} to $30^{o}C$, usually at about $5^{o}C$ in a solvent such as dichloromethane and in the presence of a base such as triethylamine.

Compounds of general formula III in which R^{20} is I may be prepared from compounds of general formula III in which R^{20} is Cl or Br by reaction with sodium iodide in a solvent such as acetone.

Compounds of formulae III and IV in which X is CR^4R^5 may also be produced by cyclising a compound of formula XXIII in which A, R^2, R^3, R^4 and R^5 are as defined in relation to formula I, R^{26} is H, Cl or Br and R^{27} is halogen such as bromine or iodine in the presence of a base such as an alkali metal alkoxide or hydride in an appropriate solvent and at temperatures of from 0°C to 70°C, suitably at ambient temperature. When the base is an alkali metal alkoxide such as sodium methoxide, then an alcohol will be a suitable solvent but when an alkali metal hydride, for example sodium hydride is chosen, it is more appropriate to choose an aprotic solvent such as THF.

Compounds of formula XXIII may be prepared from compounds of formula VI, as defined above, by reaction with a compound of formula XXIV in which R^2, R^3, R^4 and R^5 are as defined in relation to formula I and R^{26} and R^{27}

are as defined for general formula XXIII, in the presence of a base, such as triethylamine, in a solvent, such as diethyl ether, at 0°C to 100°C, suitably ambient temperature. Compounds of general formula XXIV are readily available or may be prepared by known methods, for example as described by Ikuta et al, J. Med. Chem., 30, 1995 (1987).

Compounds of general formula IV in which X is S may be prepared from derivatives of general formula VI, in which A is as defined for general formula I, by reaction with thioglycolic acid and a compound of general formula R^2R^3CO with continuous removal of water from the reaction.

In some cases, however, cyclisation does not occur or is incomplete and some or all of the product of the reaction is a compound of general formula XXX, wherein A, R^2 and R^3 are as defined for general formula I.

Compounds of general formula XXX may be cyclised to give compounds of general formula IV by treatment with a weak base such as triethylamine in an organic solvent such as dichloromethane, followed by a halogenating agent such as thionyl chloride and further treatment with weak base.

Compounds of general formula IV in which X is CH_2 may be prepared in two steps from a compound of general formula VI. Firstly, the compound of formula VI is reacted with a compound of general formula VIII in which R^2 and R^3 are as defined for general formula I to give a carboxylic acid of general formula IX in which R^2 and R^3 are as defined for general formula I. The reaction is preferably conducted at a temperature of from about 15^o to 50^oC in the presence or absence of a solvent. A method for the preparation of compounds of general formula VIII is described in Organic Synthesis, 60, 66-68.

The compound of general formula IX may be converted to the compound of general formula IV by decarboxylation which may be achieved simply by heating to the melting point and allowing decarboxylation to occur.

Alternatively compounds of formula IV in which X is CR^4R^5 may be produced from compounds of formula XXV, where A is as defined in relation to formula I and R^{13} is halogen, by reaction with a compound of formula XXVI where R^2, R^3, R^4 and R^5 are as defined in relation to formula I, in the presence of metals or metal oxides, suitably copper or copper I oxide, at temperatures of 30°C to 250°C, suitably 130°C to 180°C. Alternative procedures can include treatment of XXV with alkali metal salts of XXVI in solvents such as dimethyl sulphoxide and at temperatures of 0°C to 100°C,

suitably ambient temperatures. This route is particularly useful for compounds in which A is a heterocyclic group.

Compounds of general formula II in which X is O and R^{15} is OH may be prepared from compounds of general formula XIII, wherein A, R^2 and R^3 are as defined for general formula I and each R^{19} is, independently, benzyl or substituted benzyl; by reduction, suitably hydrogenation over a palladium or platinum catalyst, in the presence of an acid such as trifluoroacetic acid.

Compounds of general formula XIII may be prepared from compounds of general formula XIV, wherein R^{19} is as defined for general formula XIII and A is as defined for general formula I; by reaction with compounds of the formula $R^{19}OCR^2R^3X$ where X is halogen, particularly chlorine, and R^2, R^3 and R^{19} are as defined above. For optimal results, the reaction is carried out in a mixed aqueous/organic solvent such as water/dichloromethane and in the presence of a base, for example sodium hydroxide, and a phase transfer catalyst, for example tetrabutylammonium iodide.

Compounds of general formula XIV may be prepared from compounds of general formula VI by reaction with compounds of general formula XV, wherein R^{19} is as defined above for general formula XIII. Usually, the compound of general formula XV will be converted to the acid chloride using a chlorinating agent such as oxalyl chloride in the presence of N,N-dimethylformamide (DMF) before reaction with the compound of general formula VI. The reaction may take place in an organic solvent, preferably a chlorinated solvent such as dichloromethane.

Carboxylic acids of general formula XV may be prepared from esters of general formula XVI, wherein R^{19} is as defined for general formula XIII; by known methods such as treatment with aqueous potassium carbonate in a solvent such as tetrahydrofuran (THF).

Esters of general formula XVI may be prepared from dichloroacetic acid by reaction with a mixture of an alcohol of general formula $R^{19}OH$, where R^{19} is as defined above for general formula XIII, and its corresponding alkali metal alkoxide. The reaction will usually be conducted in the appropriate alcohol. All of the starting materials of this reaction are readily available.

Compounds of general formula II in which X is O and R^{15} is OH may, alternatively be synthesised from compounds of general formula XII, wherein

R^{21} is C_1-C_6 alkyl and A, R^2 and R^3 are as defined in general formula I; by reaction with an acid such as hydrochloric acid in an organic solvent such as 1,4-dioxan.

Compounds of general formula XII may be synthesised from compounds of general formula XVII, wherein A, R^2 and R^3 are as defined for general formula I, R^{21} is as defined above and R^{23} is C_1-C_6 alkyl; by a two stage reaction in which the compound is firstly treated with a strong acid such as trifluoroacetic acid and then heated with a weak base such as sodium bicarbonate.

In some cases, treatment of a compound of general formula XVII with a strong acid will result in the production of a compound of general formula II without it being necessary to isolate the intermediate of general formula XII.

Compounds of general formula XVII may be obtained by the oxidation of compounds of general formula XVIII, wherein A, R^2, R^3, R^{21} and R^{23} are as defined above using, for example, an oxidising agent such as sodium periodate. The reaction is preferably carried out in a polar solvent such as a mixture of water and an alcohol, for example methanol or ethanol, at a temperature of between 0^o and 100^oC, preferably at room temperature.

Compounds of general formula XVIII may be prepared from compounds of general formula XIX, wherein A and R^{23} are as defined above; and compounds of general formula XX, wherein R^2 and R^3 are as defined for general formula I, R^{21} is as defined for general formula XII and X is a leaving group, particularly a halogen such as chlorine. The reaction requires basic conditions which may be provided by, for example, aqueous sodium hydroxide which may be mixed with an organic solvent such as dichloromethane. In this case, a phase transfer catalyst may also be present. Ethers of general formula XX are readily available or can easily be synthesised by a skilled chemist.

Compounds of general formula XIX may be synthesised by reacting a compound of general formula VI with a compound of general formula XXXI, wherein R^{23} is as defined above and R^{22} is C_1-C_6 alkyl. Compounds such as these are readily available. It is greatly preferred that the reaction is carried out under basic conditions, for example in the presence of sodium hydride. A polar organic solvent such as DMSO may be used.

Compounds of formula II in which X is S and R^{15} is OH may prepared by solvolysis of compounds of formula XXI in which A, R^2 and R^3 are as defined in relation to formula I. The reaction is conveniently carried out in the presence of an aqueous alcohol, such as methanol, in a solvent such as dichloromethane at temperatures of from 0 to 50°C, preferably ambient temperature. The reaction often proceeds more successfully if conducted in the presence of a weak base such as sodium or potassium bicarbonate.

Compounds of formula XXI may be prepared from compounds of formula XXII, where A, R^2 and R^3 are as defined in relation to formula I, by reaction with trifluoroacetic anhydride in a solvent such as trifluoroacetic acid at temperatures of -10°C to 70°C, suitably at ambient temperature.

Compounds of formula XXII may be prepared from compounds of formula IV in which X is S, by reaction with, for example, a periodate salt. A suitable solvent is an aqueous alcohol such as ethanol or methanol and a suitable temperature is ambient. In cases where A does not contain readily oxidisable groups, one equivalent of a peracid, suitably m-chloroperbenzoic acid, in a solvent such as dichloromethane may be used.

Compounds of general formula II in which R^{15} is SH may be prepared from compounds of general formula III in which R^{20} is Br by reaction firstly with a thioacid of general formula $HS(C=O)R^1$ wherein R^1 is as defined in general formula I to give a compound of general formula I in which Y is S, W is O and n is 0, followed by reaction with ammonia in a protic solvent such as methanol. The second step is preferably carried out at a temperature of -10^{o} to $+10^{o}$C, usually about 0^{o}C.

An alternative method for the preparation of compounds of general formula I in which X is CR^4R^5, Y is O, W is O and Z is NH is by the cyclisation of a compound of general formula XXVII, wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined for general formula I and R^{25} is halogen such as chloro, bromo or iodo. The reaction requires basic conditions which may be provided by, for example, an alkali metal hydride or alkoxide. The solvent will, to a certain extent, depend on the base which is chosen with solvents such as THF being preferred for hydride bases and alcoholic solvents being more appropriate for alkoxide bases. Compounds of general formula XXVII also show herbicidal activity and form a further aspect of the invention.

Compounds of general formula XXVII may be prepared by the reaction of

a compound of general formula XXVIII, wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined for general formula I and R^{25} is as defined for general formula XXVII, with a compound of the formula R^1-N=C=O.

The reaction is similar to that described above in which a compound of general formula II is converted to a compound of general formula I by reaction with a compound of the formula R^1-N=C=O and the same or similar reaction conditions apply.

In a variation of this process, a compound of general formula I in which X is CR^4R^5, Y is O, W is O and Z is NH may be prepared from a compound of general formula XXVIII using the same steps as described above but carried out in reverse order. Thus a compound of general formula XXVIII may be cyclised to give a compound of general formula II in which R^{15} is OH using the same reaction conditions as for the cyclisation of the compound of general formula XXVII. The compound of general formula II may then be reacted with a compound of the formula R^1-N=C=O as described above to give the required compound of general formula I in which X is CR^4R^5, Y is O, W is O and Z is NH.

Compounds of general formula XXVIII may be prepared by the reaction of an aniline derivative of general formula VI with a compound of general formula VII, wherein R^2, R^3, R^4 and R^5 are as defined in general formula I, in the presence of a reagent such as boron tribromide, aluminium trichloride, tin tetrachloride or titanium tetrachloride in a solvent such as dichloromethane or dichloroethane.

Compounds of general formula XXVII in which R^{25} is iodo and A, R^2, R^3, R^4 and R^5 are as defined for general formula I may, alternatively, be prepared from compounds of formula XXIX, wherein R^1, R^2, R^3, R^4 and R^5 are as defined for general formula I. Firstly, a solution of the compound of general formula XXIX in a solvent such as dichloromethane is treated sequentially with trimethylsilyl iodide, trimethylsilyl chloride and oxalyl chloride in a one pot reaction. A compound of general formula VI may then be added to the reaction mixture in a solvent such as dichloromethane and in the presence of a base such as pyridine and, optionally, in the presence of dimethylaminopyridine (DMAP) to give a product of general formula XXVII in which R^{25} is I.

Compounds of general formula XXIX may be prepared from compounds of general formula VII as defined above by treatment with a compound of the

formula R^1-N=C=O in dichloromethane and in the presence either of triethylamine or, preferably, of boron trifluoride etherate. This reaction is similar to that described for the conversion of compounds of general formula II to compounds of general formula I and is carried out under similar conditions.

This route to compounds of general formula XXVII and then to compounds of general formula I is particularly useful for compounds in which A is a heterocyclic group and which may be difficult to prepare by other routes.

A route to compounds of general formula I in which Y is S, W is O and n is 0 has been briefly mentioned above and involves the reaction of a compound of general formula III in which R^{20} is Br by reaction with a thioacid of general formula $HSC(=O)R^1$. The reaction is preferably carried out under basic conditions, these being supplied by use of a weak base, especially an amine base such as triethylamine. The reaction may be carried out under an inert atmosphere such as nitrogen or argon at a temperature of from -20° to 5°C, preferably about 0°C.

An alternative route to compounds of general formula I is by the reaction of a compound of general formula IV with a compound of general formula $BrCR^4R^5C(=O)OR^1$, wherein R^1, R^4 and R^5 are as defined for general formula I. This reaction produces compounds of general formula I in which Y is CR^4R^5, Z is O and W is O. The reaction may be carried out in an organic solvent, for example an ether such as THF and at a temperature of from -100° to 30°C, most suitably -80° to 0°C. It is greatly preferred that the compound of general formula IV is first reacted with a strong base and bases such as lithium hexamethyldisilazide have proved to be especially suitable for the purpose. Subsequently the compound of formula $BrCR^4R^5C(=O)OR^1$ may be added to the reaction mixture. An inert atmosphere such as nitrogen or argon may also be necessary for this reaction.

Compounds of general formula I where X is CR^4R^5, Z is NR^4, W is O, Y is NH and n is 1 can be prepared from compounds of general formula XXXII on treatment with an appropriate amine HNR^4R^1 in a suitable solvent such as toluene at an appropriate temperature between 0°C and 110°C, more typically 70°C. Compounds of general formula XXXII can be prepared by a Curtius rearrangement reaction from an azide of general formula XXXIII in a suitable solvent such as toluene at an appropriate temperature between 20°C and 120°C, more typically between 90°C and 100°C.

Compounds of general formula XXXIII can be prepared from compounds of general formula IX by methods described in the literature (see March, "Advanced Organic Chemistry: Reactions, Mechanisms & Structure", 4th Edition, John Wiley & Sons, 1992, page 1092). Alternatively compounds of general formula IX can be converted to compounds of general formula XXXII in one step on treatment with a reagent such as diphenylphosphoryl azide in a suitable solvent such as toluene in the presence of a suitable base such as triethylamine at an appropriate temperature between 20°C and 120°C; more typically between 90°C and 100°C.

Compounds of general formula I in which Y is NR^6 may be prepared from compounds of formula I in which Y is NH by treatment with a base followed by alkylation using a compound of formula R^6-L, where L is a leaving group.

Compounds of general formula I in which Y is CR^4R^5 and Z is NR^4 may be prepared from compounds of general formula X in which A, X, R^2, R^3, R^4 and R^5 are as defined in general formula I by reaction with amines of general formula NHR^1R^4. It is preferable that the reaction is carried out under dry conditions in an organic solvent such as dichloromethane and at a temperature of from -20° to 30°C. It is often preferred for the reagents to be added to one another at about 0°C, following which the reaction mixture may be allowed to warm to room temperature.

Compounds of general formula X may be prepared from the parent acids, which are compounds of general formula I in which Y is CR^4R^5, Z is O and R^1 is H, by reaction with an agent such as oxalyl chloride or thionyl chloride. The reaction will generally take place under dry conditions. When thionyl chloride is used, it may be added to the compound of general formula I and the mixture heated under reflux. When oxalyl chloride is used, on the other hand, much colder conditions will generally be used with the reaction temperature being from about -20° to 20°C, generally about 0°C. A reaction solvent will also be employed in most cases with a typical solvent being a halogenated solvent such as chloroform. In many cases the reaction proceeds more rapidly in the presence of a catalytic amount of DMF.

The parent acids of general formula I in which Y is CR^4R^5, Z is O and R^1 is H may be prepared from corresponding esters of general formula I in

which Y is CR^4R^5, Z is O and R^1 is an alkyl group. The ester may be reacted with an organic acid in an organic or aqueous solvent, or with an inorganic acid in a mixture of an organic solvent, such as an alcohol, and water. When R^1 is a group such as t-butyl, a strong acid such as trifluoroacetic acid (TFA) is preferred and the reaction may be conducted in an organic solvent such as dichloromethane or chloroform, or carried out in the absence of a solvent. The reaction temperature may be from 0^o to 50^oC with room temperature being preferred.

An alternative method of preparation of parent acids of general formula I in which Y is CR^4R^5, Z is O and R1 is H is by hydrogenolysis of the corresponding esters of general formula I in which Y is CR^4R^5, Z is O and R1 is a benzyl group. The reaction is carried out under an atmosphere of hydrogen in the presence of a catalyst such as 5% or 10% palladium on charcoal in an organic solvent such as ethyl acetate, tetrahydrofuran, dioxane or an alcohol such as methanol or ethanol. The reaction will take place in the absence of an acid catalyst, but will often proceed more rapidly in the presence of a catalytic amount of an acid such as trifluoroacetic acid. Reaction temperatures may range from 0^o to 50^oC with room temperature being preferred.

An alternative synthetic route to the parent acids of general formula I, in which X is S, Y is CH_2, W is O, Z is O and R^1 H, is by reaction of a derivative of general formula VI with mercaptosuccinic acid and a compound of general formula $R^2R^3C=O$. The reaction may be carried out in a solvent such as toluene and at the reflux temperature of the solvent.

The esters of general formula I in which Y is CR^4R^5, W is O, Z is O and R^1 is an alkyl group may be converted directly to amides of general formula I in which Y is CR^4R^5 and Z is NR^4 by reaction of an amine in the presence of a Lewis acid catalyst such as aluminium trichloride. The reaction should be carried out under dry conditions in an aprotic solvent such as toluene, dichloromethane or chloroform. In some cases, halogen exchange may also occur to some extent during the reaction. For example, when the catalyst is $AlCl_3$ and one of the substituents on group A in the starting material contains a halogenated moiety such as CF_3, the product in which the substituent is CCl_3 may be isolated as well as the CF_3 containing product.

Esters of general formula I in which W is O, Z is O and Y is CR^4R^5,

with at least one of R^4 and R^5 being other than hydrogen, may be prepared from the corresponding esters of general formula I in which Y is CH_2 by reaction with a strong base such as lithium hexamethyldisilazide followed by reaction with the appropriate compound R^4-Hal where Hal is a halo substituent, typically iodo. The reaction should preferably be carried out under dry conditions at a reaction temperature of from -100° to 0°C, usually at about -78°C. Suitable reaction solvents are aprotic organic solvents such as THF. The reaction may generate both the required alkylated product and a product which has been alkylated at a different site. These products can be separated immediately if necessary but if the ester is being used as an intermediate to another compound of general formula I, the remaining reaction steps can be carried out before separation of the products if this is more convenient. If required, further alkylation can be carried out with a compound R^5-Hal to obtain a dialkylated product.

As already mentioned, esters of general formula I may be prepared from compounds of general formula IV.

A further method for the synthesis of compounds of general formula I in which X is O, Y is CH_2 or CHR^4, W is O, and Z is O is from compounds of general formula XI in which R^1 and A are as defined for general formula I. Compounds of general formula XI may be reacted with compounds of general formula $R^2R^3C=O$ in a polar solvent such as DMF and in the presence of a strong base such as an alkali or alkaline earth metal hydroxide or sodium hydride. The reaction may be carried out at a temperature of 10° to 50°C but preferably will be conducted at room temperature. The method is particularly suitable for the the synthesis of esters of general formula I in which R^1 is an alkyl group. The esters may be converted to other compounds of general formula I if required by one of the methods given above.

Fumaric esters of general formula XI where A, R^1 and R^4 are as defined in relation to formula I are prepared from the corresponding fumaric monoalkyl esters of general formula XXXV where R^1 and R^4 are as defined in relation to formula I. Fumaric monoalkyl esters of general formula XXXV are reacted with a compound of formula VI where A is defined in relation to formula I in the presence of a dehydrating agent such as dicyclohexylcarbodiimide. The reaction is conducted in an aprotic organic

solvent such as dichloromethane or chloroform, at temperatures of from 0° to 50°C with room temperature being preferred. Alternatively, fumaric esters of general formula XI where A, R^1 and R^4 are as defined in relation to formula I may be prepared by converting fumaric monoalkyl esters of general formula XXXV where R^1 and R^4 are as defined in relation to formula I to the corresponding acid chloride by treatment with thionyl chloride or oxalyl chloride by methods analogous to those described above for similar transformations, followed by reaction with the compound of general formula VI where A is defined in relation to formula I. The reaction is carried out in an organic solvent such as dichloromethane or chloroform in the presence of a base such as triethylamine. The reaction may be carried out at temperatures of from 0° to 70°C with room temperature being preferred.

Alternatively, fumaric esters of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is benzyl may be prepared from the corresponding fumaric acids of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is hydrogen. Compounds of general formula XI in which R^1 is hydrogen may be reacted with benzyl alcohol in the presence of diethyl azodicarboxylate and triphenyl phosphine. The reaction is preferably conducted in an aprotic organic solvent such as dichloromethane or chloroform at temperatures of from -20 to 50°C.

Alternatively, fumaric esters of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is t-butyl may be prepared from the corresponding fumaric acids of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is hydrogen. Compounds of general formula XI in which R^1 is hydrogen may be reacted with dimethylformamide (bis) t-butyl dimethyl acetal in an organic solvent such as toluene. The reaction may be carried out at temperatures of from room temperature to 120°C, preferably from 80° to 100°C.

Fumaric acids of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is hydrogen may be prepared from fumaric acids of general formula XI where A and R^4 are as defined in relation to formula I and R^1 is alkyl by reaction with an inorganic base such as sodium hydroxide or potassium hydroxide in an alcohol, preferably methanol or ethanol. The reaction may be carried out at temperatures of from 0° to 100°C.

Fumaric monoalkyl esters of general formula XXXV where R^1 and R^4 are as defined in relation to formula I are known compounds, or may be prepared from known compounds by standard methods.

Compounds of general formula I in which Y is NR^6 and Z is NR^4 and R^4 and R^6 form a bridge may be synthesised in a variety of ways.

Compounds in which the bridge is represented by the formula $-Q^1-C(=O)-$ may be synthesised from compounds of general formula I in which Z is NH and Y is $N-Q^1-C(=O)-L$ in which L is a leaving group such as methoxy, ethoxy, chloro and Q^1 is as defined above. The reaction is preferably carried out in the presence of a strong base such as sodium hydride, suitably in a solvent such as THF. Usually, the reaction temperature will be in the range of 0^o to 80^oC, preferably room temperature. They may alternatively be synthesised from compounds of general formula (III) in which R^{20} is a leaving group such as I or Br by reaction with an imidazolinedione of general formula XXXVI where each of R^{12} and R^{13} independently represent hydrogen or C_1-C_4 alkyl. The reaction is carried out in an organic solvent such as N,N-dimethylformamide or tetrahydrofuran, in the presence of a strong base such as sodium hydride.

Compounds in which the bridge is represented by the formula $-C(=O)-C(=O)-$ or $-C(=O)-Q^2-C-(=O)-$ may be synthesised from compounds of general formula I in which both Y and Z are NH by reaction with a compound of formula $LC(=O)-C(=O)L$ or $LC(=O)-Q^2-C(=O)L$ in which Q^2 and L are as defined above. The reaction may be carried out in an organic solvent such as toluene at a temperature of from 30^o to 120^oC. Often, the reaction will be conducted at a temperature of about 80^oC.

Compounds in which the bridge is represented by the formula -HC=CH- may be synthesised from compounds of general formula I in which Z is NH and Y is NCH_2CHL_2, wherein L is a leaving group as defined above. The reaction may be carried out in a solvent such as THF under acidic conditions which may be provided by the presence of an aqueous inorganic acid such as hydrochloric acid. The reaction temperature may be from 5^o to 50^oC but will, in most cases, be room temperature.

Compounds of general formula I in which the bridge is represented by the formula -CH=CH- may be converted to compounds of general formula I in which the bridge is represented by CH_2-CH_2 by reduction, for example hydrogenation over a palladium or platinum catalyst. Catalytic

hydrogenations may be carried out in a solvent such as ethyl acetate. The reaction usually proceeds at an acceptable rate at room temperature and at a pressure of from 1 to 5 bar.

Compounds in which the bridge is represented by the formula $-C(=O)CH_2-$ may be synthesised from compounds of general formula I in which Y and Z are both NH by reaction with CHO-CHO. The reaction may be conducted under acidic conditions which may be provided by the presence of a catalytic amount of, for example, p-toluene sulphonic acid. An example of a suitable reaction solvent is toluene and the reaction is preferably carried out under Dean and Stark conditions at a temperature of from about 80^o to 120^oC, typically at 110^oC. Similar reaction conditions may also be used for the synthesis of compounds of general formula I in which the bridge is represented by the formula $-CH_2-OCH_2-$. However, in this case, paraformaldehyde is used in place of the CHO-CHO. This particular reaction may be adapted by those skilled in the art for the synthesis of other bridged compounds.

Compounds of general formula I may be converted to other compounds of general formula I, for example by varying the substituents on the group A.

Compounds of general formula I in which X is CR^4R^5, Y and Z (if present) are other than S and A is a phenyl group having a substituent OR^{28}, wherein R^{28} is C_1-C_4 alkyl or haloalkyl, may be converted into compounds of general formula I in which the phenyl ring is disubstituted and wherein the second substituent is a halo, particularly a chloro, group by treatment with a halogenating agent such as N-chlorosuccinimide in a solvent such as N,N-dimethylformamide (DMF). The reaction may be carried out at a temperature of from 15^o to 80^oC, more usually at from 20^o to 60^oC. When the group OR^{28} is at the 3-position, the major product of the reaction is usually the 3,4-substituted compound with the 3,6-substituted compound being the minor product.

Compounds of general formula I wherein X is CR^4R^5, Y and Z (if present) are other than S and the group A is a phenyl group with an $S(C_1$-C_4 alkyl) or $S(C_1$-C_4 haloalkyl) substituent may be oxidised to give compounds of general formula I with the corresponding sulfoxide substituent on the A group. The oxidation may be carried out using, for example, one equivalent of an agent such as metachloroperbenzoic acid (MCPBA) in a halogenated solvent, for example chloroform. The reaction is preferably conducted at a

temperature of from 0°C to room temperature.

A similar process may be used to obtain the equivalent sulfone. In this case, however, two equivalents of MCPBA may be used and the reaction mixture is preferably heated to a temperature of from 30° to 90°C, usually to the reflux temperature of the solvent employed.

The functional groups $CO(Z)_m R^1$ may be inter-converted to different functional groups using techniques of esterification, transesterification, hydrolysis and amidation some of which are discussed above. Other such methods are standard procedures well known to the skilled chemist.

Variations of the above procedures will be apparent to the skilled chemist as well as alternative processes for preparing the compounds of the invention. Other methods for making the compounds of the present invention are analagous to the methods described in WO-A-9413652.

The compounds of formula I above are active as herbicides, and the invention therefore provides, in a further aspect, a process for severely damaging or killing unwanted plants, which process comprises applying to the plants, or to the growth medium of the plants, a herbicidally effective amount of a compound of formula I as hereinbefore defined.

The compounds of formula I are active against a broad range of weed species including monocotyledonous and dicotyledonous species. They show some selectivity towards certain species; they may be used, for example, as selective herbicides in soya, rice and maize crops. The compounds of formula I are applied directly to unwanted plants (post-emergence application) but they are preferably applied to the soil before the unwanted plants emerge (pre-emergence application).

The compounds of formula I may be used on their own to kill or severely damage plants, but are preferably used in the form of a composition comprising a compound of formula I in admixture with a carrier comprising a solid or liquid diluent.

Compositions containing compounds of formula I include both dilute compositions, which are ready for immediate use, and concentrated compositions, which require to be diluted before use, usually with water. Preferably the compositions contain from 0.01% to 90% by weight of the active ingredient. Dilute compositions ready for use preferably contain from 0.01 to 2% of active ingredient, while concentrated compositions may

contain from 20 to 90% of active ingredient, although from 20 to 70% is usually preferred.

The solid compositions may be in the form of granules, or dusting powders wherein the active ingredient is mixed with a finely divided solid diluent, e.g. kaolin, bentonite, kieselguhr, dolomite, calcium carbonate, talc, powdered magnesia, Fuller's earth and gypsum. They may also be in the form of dispersible powders or grains, comprising a wetting agent to facilitate the dispersion of the powder or grains in liquid. Solid compositions in the form of a powder may be applied as foliar dusts.

Liquid compositions may comprise a solution or dispersion of an active ingredient in water optionally containing a surface-active agent, or may comprise a solution or dispersion of an active ingredient in a water-immiscible organic solvent which is dispersed as droplets in water.

Surface-active agents may be of the cationic, anionic, or non-ionic type or mixtures thereof. The cationic agents are, for example, quaternary ammonium compounds (e.g. cetyltrimethylammonium bromide). Suitable anionic agents are soaps; salts of aliphatic mono ester of sulphuric acid, for example sodium lauryl sulphate; and salts of sulphonated aromatic compounds, for example sodium dodecylbenzenesulphonate, sodium, calcium, and ammonium lignosulphonate, butylnaphthalene sulphonate, and a mixture of the sodium salts of diisopropyl and triisopropylnaphthalenesulphonic acid. Suitable non-ionic agents are the condensation products of ethylene oxide with fatty alcohols such as oleyl alcohol and cetyl alcohol, or with alkylphenols such as octyl- or nonyl- phenol (e.g. Agral 90™) or octyl-cresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, for example sorbitan monolaurate; the condensation products of the partial ester with ethylene oxide; the lecithins; and silicone surface active agents (water soluble surface active agents having a skeleton which comprises a siloxane chain e.g. Silwet L77™). A suitable mixture in mineral oil is Atplus 411F™.

The aqueous solutions or dispersions may be prepared by dissolving the active ingredient in water or an organic solvent optionally containing wetting or dispersing agent(s) and then, when organic solvents are used, adding the mixture so obtained to water optionally containing wetting or dispersing agent(s). Suitable organic solvents include, for example, ethylene di-chloride, isopropyl alcohol, propylene glycol, diacetone

alcohol, toluene, kerosene, methylnaphthalene, the xylenes and trichloroethylene.

The compositions for use in the form of aqueous solutions or dispersions are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, and the concentrate is then diluted with water before use. The concentrates are usually required to withstand storage for prolonged periods and after such storage, to be capable of dilution with water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. Concentrates conveniently contain 20-90%, preferably 20-70%, by weight of the active ingredient(s). Dilute preparations ready for use may contain varying amounts of the active ingredient(s) depending upon the intended purpose; amounts of 0.01% to 10.0% and preferably 0.1% to 2%, by weight of active ingredient(s) are normally used.

A preferred form of concentrated composition comprises the active ingredient which has been finely divided and which has been dispersed in water in the presence of a surface-active agent and a suspending agent. Suitable suspending agents are hydrophilic colloids and include, for example, polyvinylpyrrolidone and sodium carboxymethylcellulose, and the vegetable gums, for example gum acacia and gum tragacanth. Preferred suspending agents are those which impart thixotropic properties to, and increase the viscosity of the concentrate. Examples of preferred suspending agents include hydrated colloidal mineral silicates, such as montmorillonite, beidellite, nontronite, hectorite, saponite, and saucorite. Bentonite is especially preferred. Other suspending agents include cellulose derivatives and polyvinyl alcohol.

The rate of application of the compounds of the invention will depend on a number of factors including, for example, the compound chosen for use, the identity of the plants whose growth is to be inhibited, the formulations selected for use and whether the compound is to be applied for foliage or root uptake. As a general guide, however, an application rate of from 0.001 to 20 kilograms per hectare is suitable while from 0.025 to 10 kilograms per hectare may be preferred.

The compositions of the invention may comprise, in addition to one or more compounds of the invention, one or more compounds not of the invention

but which possess biological activity. Accordingly in yet a still further embodiment the invention provides a herbicidal composition comprising a mixture of at least one herbicidal compound of formula I as hereinbefore defined with at least one other herbicide.

The other herbicide may be any herbicide not having the formula I. It will generally be a herbicide having a complementary action in the particular application.

Examples of useful complementary herbicides include:

A. benzo-2,1,3-thiadiazin-4-one-2,2-dioxides such as bentazone;

B. hormone herbicides, particularly the phenoxy alkanoic acids such as MCPA, MCPA-thioethyl, dichlorprop, 2,4,5-T, MCPB, 2,4-D, 2,4-DB, mecoprop, trichlopyr, clopyralid, and their derivatives (eg. salts, esters and amides);

C. 1,3 dimethylpyrazole derivatives such as pyrazoxyfen, pyrazolate and benzofenap;

D. Dinitrophenols and their derivatives (eg. acetates) such as dinoterb, dinoseb and its ester, dinoseb acetate;

E. dinitroaniline herbicides such as dinitramine, trifluralin, ethalflurolin, pendimethalin, oryzalin;

F. arylurea herbicides such as diuron, flumeturon, metoxuron, neburon, isoproturon, chlorotoluron, chloroxuron, linuron, monolinuron, chlorobromuron, daimuron, methabenzthiazuron;

G. phenylcarbamoyloxyphenylcarbamates such as phenmedipham and desmedipham;

H. 2-phenylpyridazin-3-ones such as chloridazon and norflurazon;

I. uracil herbicides such as lenacil, bromacil and terbacil;

J. triazine herbicides such as atrazine, simazine, aziprotryne, cyanazine, prometryn, dimethametryn, simetryne, and terbutryn;

K. phosphorothioate herbicides such as piperophos, bensulide, and butamifos;

L. thiolcarbamate herbicides such as cycloate, vernolate, molinate, thiobencarb, butylate*, EPTC*, tri-allate, di-allate, esprocarb, tiocarbazil, pyridate, and dimepiperate;

M. 1,2,4-triazin-5-one herbicides such as metamitron and metribuzin;

N. benzoic acid herbicides such as 2,3,6-TBA, dicamba and chloramben;

O. anilide herbicides such as pretilachlor, butachlor, alachlor, propachlor, propanil, metazachlor, metolachlor, acetochlor, and dimethachlor;

P. dihalobenzonitrile herbicides such as dichlobenil, bromoxynil and ioxynil;

Q. haloalkanoic herbicides such as dalapon, TCA and salts thereof;

R. diphenylether herbicides such as lactofen, fluroglycofen or salts or ester thereof, nitrofen, bifenox, aciflurofen and salts and esters thereof, oxyfluorfen, fomesafen, chlornitrofen and chlomethoxyfen;

S. phenoxyphenoxypropionate herbicides such as diclofop and esters thereof such as the methyl ester, fluazifop and esters thereof, haloxyfop and esters thereof, quizalofop and esters thereof and fenoxaprop and esters thereof such as the ethyl ester;

T. cyclohexanedione herbicides such as alloxydim and salts thereof, sethoxydim, cycloxydim, tralkoxydim, and clethodim;

U. sulfonyl urea herbicides such as chlorosulfuron, sulfometuron, metsulfuron and esters thereof; benzsulfuron and esters thereof such as DPX-M6313, chlorimuron and esters such as the ethyl ester thereof pirimisulfuron and esters such as the methyl ester thereof, 2-[3-(4-methoxy-6-methyl-1,3,5-triazin-zyl)-3-methylureidosulphonyl) benzoic acid esters such as the methyl ester thereof (DPX-LS300) and pyrazosulfuron;

V. imidazolidinone herbicides such as imazaquin, imazamethabenz, imazapyr and isopropylammonium salts thereof, imazethapyr;

W. arylanilide herbicides such as flamprop and esters thereof, benzoylprop-ethyl, diflufenican;

X. amino acid herbicides such as glyphosate and glufosinate and their salts and esters, sulphosate and bialaphos;

Y. organoarsenical herbicides such as monosodium methanearsonate (MSMA);

Z. herbicidal amide derivative such as napropamide, propyzamide, carbetamide, tebutam, bromobutide, isoxaben, naproanilide and naptalam;

AA. miscellaneous herbicides including ethofumesate, cinmethylin, difenzoquat and salts thereof such as the methyl sulphate salt, clomazone, oxadiazon, bromofenoxim, barban, tridiphane, flurochloridone, quinchlorac, mefanacet, and triketone herbicides such as sulcotrione;

BB. Examples of useful contact herbicides include: bipyridylium herbicides such as those in which the active entity is paraquat and those in which the active entity is diquat;

* These compounds are preferably employed in combination with a safener such as dichlormid.

The invention is illustrated by the following Examples. The abbreviations used in the Examples have the following meanings:

-THF = tetrahydrofuran

-DMF = N,N-dimethylformamide

-HPLC = High Performance Liquid Chromatography

-NMR = Nuclear Magnetic Resonance (performed at 270MHz and in CDCl3 as solvent unless otherwise stated). The following abbreviations are used to indicate the multiplicity of the peaks in the NMR spectrum: s (singlet); d (doublet); t (triplet); q (quartet); quin (quintet); m (multiplet); br (broad).

-ppm = parts per million

-m.p. = melting point

-Chromatography on columns of silica gel, unless specified

-Solutions dried over magnesium sulfate, unless specified

-Solutions were concentrated under reduced pressure

-IR spectrum: infra-red absorption spectrum.

-MS: mass spectrum

-GC: gas chromatography

-TLC: thin layer chromatography

-b.p: boiling point

EXAMPLE 1 **Preparation of Compound 1: 5-t-Butylcarbamoylamino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone.**

Step 1 Preparation of 3-(3-trifluoromethyl)phenyl-4-thiazolidinone

A stirred solution of 3-trifluoromethylaniline (43.50g) in toluene (275ml) was treated with thioglycolic acid (24.90g). After 10 minutes, the solution was treated dropwise with 37% aqueous formaldehyde (20.8ml), followed by p-toluenesulphonic acid (30mg). The mixture was then heated under reflux, and water was collected in a Dean and Stark apparatus. After 23.5ml of water had been collected, the mixture was cooled, extracted with ether (2x100ml) and the combined extracts washed with saturated aqueous sodium bicarbonate solution (100ml) and dried ($MgSO_4$). Evaporation under reduced pressure left a yellow oil, which afforded the title compound as a white solid on trituration with hexane, yield 44.50g, mp 59-60°C.

^1H nmr ($CDCl_3$): δ 3.76 (2H, s), 4.85 (2H, s), 7.47-7.58 (2H, m), 7.68-7.76 (2H, m).

Step 2 Preparation of 5-chloro-3-(3-trifluoromethyl)phenyl-4-thiazolidinone.

A stirred solution of 3-(3-trifluoromethyl)phenyl-4-thiazolidinone (prepared as in Step 1 above) (10.00g) in dichloromethane (150ml) was cooled in an ice bath. A stream of nitrogen was bubbled through the solution, and a solution of sulphuryl chloride (5.47g) in dichloromethane (5ml) was added dropwise. After the addition the solution was allowed to warm to room temperature, and was stirred for a further 1 hour whilst maintaining the nitrogen flow. The solution was evaporated under reduced pressure to leave the product as a solid residue. This product was used directly in subsequent reactions.

^1H nmr ($CDCl_3$): δ4.72(1H,d); 5.24(1H,d); 5.77(1H,s); 7.50-7.61(2H,m); 7.70-7.82(2H,m).

Step 3 Preparation of 5-azido-3-(3-trifluoromethyl)phenyl-4-thiazolidinone.

A stirred solution of 5-chloro-3-(3-trifluoromethylphenyl)-4-thiazolidinone from Step 2 (3.80g) in dimethylformamide (40ml) was treated with sodium azide (0.88g). After stirring for 10 minutes brine was added, and the resulting mixture was extracted with diethylether (2x50ml). The combined ether extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo to leave a brown oil. This was separated by silica gel chromatography, eluting with ethyl acetate/hexane mixtures, to afford the title compound, yield 3.60g.

^1H NMR ($CDCl_3$): δ 4.73(1H,d); 5.07(1H,d); 5.40(1H,s); 7.51-7.60(2H,m); 7.69-7.77(2H,m). MS: m/e 288(M^+).

Step 4 Preparation of 5-amino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone

A solution of 5-azido-N-trifluoromethyl)phenyl-4-thiazolidinone (prepared as in Step 3) (1.00g) in triethylamine (1.4ml) was stirred under a nitrogen atmosphere, and treated with 1,3-propanedithiol (1.00ml). The mixture was stirred for a further 1 hour, and was then dissolved in diethyl ether. This solution was washed with brine, dried ($MgSO_4$) and evaporated in vacuo to leave an oil. This was separated by silica-gel chromatography eluting with ethyl acetate/hexane mixtures, to afford the title compound as a colourless oil which slowly crystallised on standing, yield 0.77g. ^1H NMR ($CDCl_3$): δ 2.12(2H,broad s), 4.72(1H,d); 4.83(1H,d); 5.08(1H,s); 7.49-7.60(2H,m); 7.70-7.79(2H,m).

Step 5 Preparation of 5-t-butylcarbamoylamino-3-(3-trifluoromethyl) phenyl-4-thiazolidinone

A stirred solution of 5-amino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone from Step 4 (0.655g) in triethylamine (0.38ml) was treated with t-butyl isocyanate (0.272g). After stirring for a further 30 minutes, the solid was broken up under hexane, and filtered off to leave an off-white solid, which was recrystallised from toluene. The resultant solid was added to

chloroform (40ml), and the mixture was heated to reflux when the insoluble material (A) was filtered off. On cooling the filtrate, a precipitate formed, which was filtered off (B). Solid samples (A) and (B), the title compound, were combined, yield 0.249g, m.p. 203-204°C. ^{1}H NMR ($CDCl_3$): δ 1.30(9H,s); 4.78(1H,d); 4.89(1H,d); 5.53(1H,s); 5.73(1H,d); 6.42(1H,d); 7.45-7.58(2H,m); 7.69(1H,d); 7.82(1H,d).

The procedures described in Steps 3 to 5 were also used to prepare Compounds 28 (m.p. 175-176°C), 53 (m.p. 175-176.5°C) and 55 (m.p. 155-157°C) of Table I.

EXAMPLE 2 **Preparation of Compound 2: 5-Isopropyloxycarbonylamino-3-(3--trifluoromethyl)phenyl-4-thiazolidinone**

A solution of 5-amino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone (prepared as in steps 1 to 4 of Example 1) (0.655g) in dry toluene (2.5ml) was stirred under a nitrogen atmosphere, and treated with triethylamine (0.38ml). The resultant solution was cooled to 0°C, and a solution of isopropyl chloroformate in toluene (1.0M; 2.5ml) was added. A precipitate began to form. The mixture was allowed to warm to room temperature, and the precipitate was filtered off and dried to afford the title compound as a white solid, yield 0.350g, m.p. 187-188°C. ^{1}H NMR ($CDCl_3$): δ 1.23(3H,d); 1.25(3H,d); 4.78(1H,d); 4.87-5.00(2H,m); 5.61 (2H,s); 7.49-7.59(2H,m); 7.67-7.80(2H,m). MS: m/e 348 (M^+).

EXAMPLE 3 **Preparation of Compound 3: 5-t-Butanoylamino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone**

A stirred solution of 5-amino-3-(3-trifluoromethyl)phenyl-4-thiazolidinone (prepared as in steps 1 to 4 of Example 1) (0.800g) in toluene (5ml) was treated sequentially with triethylamine (0.42ml) then pivaloyl chloride (0.37ml). The mixture was stirred for 4 hours, then the precipitate was filtered off. This was recrystallised from chloroform/petrol to remove triethylammonium hydrochloride, and the material from the mother liquors was recrystallised from chloroform/petrol to afford the title compound as a white solid, yield 0.285g, m.p. 136-137°C. ^{1}H NMR ($CDCl_3$): δ 1.24(9H,s);

4.78(1H,d); 4.97(1H,d); 5.62(1H,d); 6.58(1H,d); 7.47-7.58(2H,m); 7.71(1H,m); 7.78(1H,s).

EXAMPLE 4 **Preparation of Compound 4: 5-t-Butanoyloxy-3-(3-trifluoromethyl)phenyl-4-thiazolidinone.**

Step 1 Preparation of 5-hydroxy-3-(3-trifluoromethyl)phenyl--4-thiazolidinone

A stirred solution of 5-chloro-3-(3-trifluoromethyl)phenyl-4-thiazolidinone (from Step 2 of Example 1) in tetrahydrofuran (100ml) was treated with aqueous sodium bicarbonate solution (100ml), and the mixture was stirred vigorously for 3 hours. The organic layer was separated, diluted with ethyl acetate (50ml), washed with brine (50ml), then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a gum. Trituration with hexane afforded a buff solid, which was recrystallised from ethyl acetate/hexane to give the title compound as a white crystalline solid, yield 7.08g, mp 87-88°C. ^1H NMR ($CDCl_3$): δ 4.70(1H,d); 5.00(1H,d); 5.74(1H,s); 7.48-7.59(2H,m); 7.64-7.76(2H,m).

Step 2 Preparation of 5-t-Butanoyloxy-3-(3-trifluoromethyl)-phenyl-4-thiazolidinone.

A stirred solution of 5-hydroxy-3-(3-trifluoromethyl)phenyl-4-thiazolidione from Step 1 (0.110g) in chloroform (10ml) was cooled to 0°C and treated with triethylamine (0.056ml) followed by pivaloyl chloride (0.052ml). The mixture was stirred for 3 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate, then dried ($MgSO_4$). Evaporation of the solvent *in vacuo* left the title compound as a clear gum, yield 0.121g. ^1H NMR ($CDCl_3$): δ 1.25(9H,s); 4.69(1H,d); 5.12(1H,dd); 6.18(1H,d); 7.49-7.61(2H,m); 7.73-7.80(2H,m).

EXAMPLE 5 **Preparation of Compound 5: 5-(3,3-Dimethylbutanoyloxy)-3-(3-trifluoromethyl)phenyl-4-thiazolidinone**

By a procedure similar to that described in Example 4 but using 5-hydroxy-3-(3-trifluoromethyl)phenyl-4-thiazolidinone (prepared as in Step 1 of Example 4) (0.200g), 3,3-dimethylbutanoyl chloride (0.106ml), triethylamine (0.106ml) and dichloromethane (10ml) as solvent, the title compound was obtained as a clear gum, yield 0.257g. ^{1}H NMR ($CDCl_3$): δ 1.07(9H,s); 2.31(2H,s); 4.70(1H,d); 5.09(1H,dd); 6.12(1H,d); 7.49-7.59(2H,m); 7.72-7.79(2H,m).

The procedure of this example was also used for the synthesis of Compounds 29 (m.p. 138-139°C), 51 (m.p. 66.5-68.5°C), 54 (m.p. 135-136°C), 63 (gum), 72 (gum), 89 (m.p. 72-73°C), 96 (m.p. 115-116°C), 97 (m.p. 87-88°C), 102 (m.p. 69-71°C), 103 (m.p. 91-93°C), 104 (gum), 110 (gum), 113 (solid gum), 123, 125, 126 305, 306, 307, 310, 313, 322, 324 and 325 of Table 1.

EXAMPLE 6 **Preparation of Compound 6: N-t-Butyl-[3-(3-trifluoromethyl) phenyl-4-thiazolidinone-5-yl]acetamide**

Step 1 Preparation of [3-(3-trifluoromethyl)phenyl-4-thiazolidinone-5-yl]acetyl chloride.

2-[3-(3-trifluoromethylphenyl)-4-thiazolidinone-5-yl]acetic acid (1.45g) (prepared as in Example 14 below) was placed in a flask equipped with a stirrer bar, a reflux condenser and a silica gel drying tube. Thionyl chloride (2.25ml) was added and the reaction mixture taken slowly to reflux. After 1.5 hours at reflux, the dark coloured reaction mixture was allowed to cool to room temperature and the excess thionyl chloride was removed under reduced pressure to give the crude acid chloride as a dark oil. ^{1}H NMR ($CDCl_3$): δ 3.55(1H,dd); 3.74(1H,dd); 4.29(1H,m); 4.82(2H,m); 7.50-7.75(4H,m). IR (film): 1790cm^{-1}, 1690cm^{-1}.

Step 2 Preparation of N-t-Butyl-[3-(3-trifluoromethyl)phenyl-4-thiazolidinone-5-yl]acetamide.

The crude acid chloride from Step 1 was dissolved in dry dichloromethane (30ml) and was stirred at 0°C. t-Butylamine (1.05ml) was then added. Much

fuming occurred and the reaction mixture was allowed to stir at room temperature overnight. The following day, a further portion of t-butylamine (0.5ml) was added and after 1 hour, the reaction mixture was diluted with dichloromethane and washed successively with 2M aqueous HCl, sat. $NaHCO_3$ (aq) and water. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give the crude product as a brown solid. Purification by flash chromatography on silica, eluting with ethyl acetate in hexane (a gradient of 35% to 40% ethyl acetate), gave a yellow solid which was recrystallised from ethyl acetate/hexane to give the pure title compound as a light yellow solid (0.56g) m.p. 144.5-145.5°C. ^1H NMR ($CDCl_3$): δ 1.35(9H,s); 2.69(1H,dd), 2.98(1H,dd); 4.29(1H,m); 4.80(2H,m); 5.52(1H,brs); 7.53(2H,m); 7.74(2H,m). M.S. m/e.

EXAMPLE 7 **Preparation of Compound 7: t-Butyl [1-(3-trifluoromethyl) phenyl-2-pyrrolidinone-3-yl]acetate**

Step 1 Preparation of 1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-carboxylic acid

A suspension of 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (prepared as described in Organic Syntheses, Volume 60, p66-68) (8.00g) in 3-trifluoromethylaniline (8.05g) was stirred at room temperature for 24 hours. The mixture was filtered, and the insoluble solid was washed with chloroform. The combined filtrates were washed with 2M hydrochloric acid, brine and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a brown solid, which was recrystallised from chloroform/hexane to give the product as a white, crystalline solid, yield 4.10g, mp 135-136°C (dec).

^1H nmr ($CDCl_3$): δ 2.47-2.67 (2H, m), 3.70 (1H, t), 3.92-4.01 (2H, m), 7.00 (broad), 7.45-7.60 (2H, m), 7.81-7.90 (2H, m)

Step 2 Preparation of 1-(3-trifluoromethyl)phenyl-2-pyrrolidinone

1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-carboxylic acid from Step 1 (3.60g) was heated to its melting point, and heating was continued until effervescence ceased (ca 50 minutes). The melt was cooled, dissolved in

diethyl ether, and treated with decolourising charcoal. The charcoal was filtered off, and the solvent was removed under reduced pressure to leave a solid residue. This was recrystallised from hexane to give the product as colourless needles, yield 2.20g, mp 67-68°C.

^{1}H nmr ($CDCl_3$): δ2.19 (2H, quin), 2.62 (2H, t), 3.89 (2H, t), 7.35-7.53 (2H, m), 7.81-7.93 (2H, m)
MS: m/e 229 (M^+)

Step 3 Preparation of t-Butyl-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetate

A solution of lithium hexamethyldisilazide (7.86ml, 1.0M) in THF was added via syringe to 1-(3-Trifluoromethyl)phenyl-2-pyrrolidinone from Step 2 (1.5g) in THF (15ml) at -78°C under a nitrogen atmosphere. The yellow solution was stirred at -78°C for 30 minutes, followed by rapid addition of t-butylbromoacetate (1.58ml) via syringe. After 20 minutes, the reaction was allowed to warm slowly to room temperature before pouring into water (100ml) and extracting with ethyl acetate (2x100ml). The combined extracts were washed with brine (100ml), dried (Na_2SO_4) and evaporated in vacuo. Purification of the residue by flash chromatography on silica, eluting with 40% ethyl acetate in hexane, gave the title compound as a yellow oil (0.91g). ^{1}H NMR ($CDCl_3$): δ 1.46(9H,s); 1.94(1H,m); 2.48(1H,dd) overlapping 2.49(1H,m); 2.89(1H,dd); 3.13(1H,m); 3.84(2H,m); 7.39(1H,d); 7.49(1H,dd); 7.89(1H,s) overlapping 7.90(1H,d). M.S. m/e 344 (MH^+).

EXAMPLE 8 **Preparation of Compound 8: N-t-Butyl-[1-(3-trifluoromethyl) phenyl-2-pyrrolidinone-3-yl]acetamide**

Oxalyl chloride (0.127ml) was added via syringe to a suspension of 2-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetic acid (0.380g) (prepared as in Example 13 below) in chloroform (15ml) at room temperature. Dimethylformamide (1 drop) was added and stirring continued for 90 minutes during which time the effervescence stopped and the solid dissolved. t-Butyl amine (0.41ml) was added dropwise at 0°C causing an instant precipitate. The reaction mixture was diluted with chloroform (100ml) and

washed with water (100ml), dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography on silica, eluting with ethyl acetate gave the amide contaminated with a little of the starting acid. The solid was dissolved in ether (100ml) washed with sat. $NaHCO_3$ (aq) (50ml), dried (Na_2SO_4) and evaporated in vacuo to give the pure title compound (0.270g) as a colourless crystalline solid, m.p;. 127-129°C. ^1H NMR ($CDCl_3$): δ 1.33(9H,s); 1.99(1H,m); 2.37(1H,dd); 2.51(1H,m); 2.71(1H,dd); 3.05(1H,m); 3.83(2H,m); 5.98(1H,brs); 7.41(1H,d); 7.49(1H,t); 7.87(1H,d) overlapping 7.89(1H,s). M.S.: m/e 342 (M^+).

The procedure of this example was also used in the synthesis of Compound 16 (m.p. 128-129°C), Compound 22 (m.p. 137-138°C), Compound 23 (m.p. 110°C) and Compound 31 (m.p. 87-90°C) of Table 1.

EXAMPLE 9 **Preparation of Compound 9: 3-(2-Pyrrolylcarbonyloxy)-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone**

Step 1 Preparation of 3-hydroxy-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone

A stirred solution of 1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (prepared as in Steps 1 and 2 of Example 7 above) (1.10g) in dry tetrahydrofuran (5ml) was cooled to -70°C under a nitrogen atmosphere, and a solution of lithium hexamethyldisilazide in hexane (1.0M, 4.9ml) was added dropwise. The resultant pale yellow suspension was then treated with a solution of N-toluenesulphonyl-3-phenyloxaziridine (prepared as described in Journal of Organic Chemistry, (1988), 53, 2087) (2.00g) in dry tetrahydrofuran (5ml). The resultant pale yellow solution was allowed to warm to room temperature, and was then quenched with water and acidified to pH5 using 2M hydrochloric acid. The mixture was extracted with diethyl ether (x2), and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to leave an oil. Purification by silica gel chromatography, eluting with ethyl acetate/hexane mixtures, afforded the title compound as a clear gum, yield 0.26g.

^{1}H nmr ($CDCl_3$): δ1.62 (1H,broad s); 2.12(1H, m); 2.63(1H, m); 3.72-3.90 (2H, m); 4.51(1H, m); 7.39-7.58(2H, m); 7.77-8.02(2H, m).
MS: m/e 245 (M^+)

Step 1a Alternative Preparation of 3-hydroxy-1-(3-trifluoromethyl)phenyl-2--pyrrolidinone

Alpha-hydroxy-delta-butyrolactone (2.04g) and 3-trifluoromethylaniline (2.74ml) were heated without solvent to 100°C with stirring. After 4 hours, the temperature was raised to 150°C (oil bath temperature) and stirring was continued for a further 20 hours. After cooling, the dark red liquid was taken up in dichloromethane (5ml) and applied to a silica flash column. Elution with ethyl acetate in hexane (a gradient of 40-60% ethyl acetate) gave the title compound as a pale orange crystalline solid (2.42g).

Physical data identical to that observed for the material prepared in Step 1.

Step 1b Further alternative route for the preparation of 3-hydroxy-1(3-trifluoromethylphenyl)pyrrolidin-2-one

i) Preparation of 4-chloro-2-hydroxy-N(3-trifluoromethylphenyl)butanamide

Titanium tetrachloride (11.0ml, 1.0M solution of dichloromethane) was added dropwise to a stirred solution of 3-hydroxytetrahydrofuran-2-one (1.0g) and 3-trifluoromethylanine (1.58g) in dry 1,2-dichloroethane (20ml). After the initial exotherm had subsided, the mixture was heated under reflux for five hours, cooled and stirred vigorously for thirty minutes with an aqueous solution of ethylenediaminetetraacetic acid. It was then extracted several times with dichloromethane. The extracts were washed with hydrochloric acid (2M) and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (49:1) to give the title compound (0.63g, m.p. 98-100°C). NMR ($CDCl_3$): δ 2.2(1H,m); 2.5(1H,m); 3.35(1H,bd); 3.8(2H,m); 4.5(1H,m); 7.4(2H,m); 7.75(1H,d); 7.9(1H,s); 8.7(1H,bs).

The corresponding diol (0.08g) was also obtained as a colourless gum. It too can be conceived of as an intermediate. The use of other Lewis acids gave similar results: aluminium chloride gave chloride-diol (1:4), stannic chloride and titanium tetraisopropoxide gave diol, zinc chloride gave chloride-diol (1:2) and magnesium bromide have bromide-diol (9:1).

ii) Preparation of 4-bromo-2-hydroxy-N(3-trifluoromethylphenyl)butanamide.

Boron tribromide (11.0ml, 1.0M solution in dichloromethane was added dropwise to a stirred solution of 3-hydroxytetrahydrofuran-2-one (1.0g) and 3-trifluoromethylphenylaniline (1.58g) in 1,2-dichloroethane (20ml). The mixture was stirred overnight at room temperature, poured on to water and extracted with dichloromethane. The extracts were washed with hydrochloric acid (2M) and brine, dried over magnesium sulphate, and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane ethanol (49:1) as eluant, to give the title compound (0.74g, m.p. 67-69°C). NMR ($CDCl_3$): δ 2.3(1H,m); 2.6(1H,m); 3.5(1H,bs); 3.6(2H,dd); 4.5(1H,dd); 7.4(2H,m); 7.7 (1H,d); 7.9(1H,s); 8.7(1H,bs). MS: M^+ 325, 327.

iii) Preparation of 3-hydroxy-1(3-trifluoromethylphenyl)pyrrolidin-2-one.

Sodium hydride (0.016g, 60% suspension in mineral oil) was added to a stirred solution of the substrate (0.10g, prepared as described in Step (i) above) in dry tetrahydrofuran (10ml), whilst maintaining the temperature below 5°C. The mixture was stirred for fifteen minutes, diluted with water and extracted with dichloromethane. The extracts were washed with brine, dried over magnesium sulphate, and evaporated under reduced pressure to give the title compound (0.08g). NMR ($CDCl_3$): δ 2.1(1H,m); 2.6(1H,m); 3.4(1H,bs); 3.75(2H,m); 4.5(1H,t); 7.4(2H,m); 7.8(2H,m). This material was identical to that prepared by an alternative method in WO94/13652, Preparative Example 42, Step 3.

The bromoalcohol, prepared as described in Step (ii) above, can be used in similar fashion.

Step 2 Preparation of 2-Pyrrole carboxylic acid chloride.

Oxalyl chloride (0.48ml) was added to a suspension of 2-pyrrole carboxylic acid (0.45g) in chloroform (10ml) at room temperature. After 2 hours, effervescence had ceased and the solvent was evaporated in vacuo to give a solid. Trituration with hexane left the crude crystalline acid chloride which was used directly.

Step 3 Preparation of 3-(2-Pyrrolylcarbonyloxy)-1-(3-trifluoromethyl)-phenyl-2-pyrrolidinone.

2-Pyrrole carboxylic acid chloride from Step 2 (0.25g) was dissolved in dichloromethane (10ml) along with 3-hydroxy-1-(3-trifluoro-methyl)phenyl-2-pyrrolidinone (0.38g) from Step 1. Triethylamine (0.26ml) was added. The solution turned reddish-orange and was left stirring overnight at room temperature. After diluting with dichloromethane (100ml), the solution was washed with sat. $NaHCO_3$ (aq) (2x50ml), brine (50ml), dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography on silica, eluting with 30% ethyl acetate in hexane, gave a pale yellow oil which crystallised. Re-crystallisation from ethyl acetate/hexane gave the pure title compound (0.21g) as colourless crystals, m.p. 127.5-128°C. ^1H NMR ($CDCl_3$): δ 2.30(1H,m); 2.81(1H,m); 3.94(2H,m); 5.68(1H,t); 6.30(1H,m); 7.00(1H,m); 7.04(1H,m); 7.45(1H,d); 7.53(1H,t); 7.94(1H,d) overlapping 7.95(1H,s); 9.20(1H,brs).

EXAMPLE 10 **Preparation of Compound 10: 3-(t-Butylcarbamoyl-N-methyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

Step 1 Preparation of 3-bromo-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone

A 200ml 3 necked flask was equipped with stoppers, dropping funel, thermometer, nitrogen bubbler and magnetic stirrer. The flask was charged with 15.0g of 1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (prepared as described in Steps 1 and 2 of Example 7), phosphorus tribromide (1.0ml) and chlorobenzene (65ml). This was heated to 105°C. The dropping funnel was charged with bromine (10.6g) and this was added over a 70 minute period.

After 165 minutes, the reaction was cooled and left at room temperature for 16 hours. Tlc indicated incomplete reaction, so the mixture was heated to 105°C and a further quantity of bromine (0.73g) added. After 100 minutes, the reaction was cooled and washed with 75% $Na_2S_2O_3$ solution (3x25ml), dried over $MgSO_4$ and evaporated to give 17.7g of material which crystallised. The solid was recrystallised twice from 25ml of methanol giving the pure title compound as a crystalline solid (9.0g), mp 82-87°C.

Step 1a Alternative Preparation of 3-bromo-1-(3-trifluoromethyl)-phenyl-2-pyrrolidinone

By a procedure similar to that of Example 68 below, but using 3-trifluoromethylaniline, were prepared successively 2,4-dibromo-N(3-trifluoromethylphenyl)butanamide and 3-bromo-1(3-trifluoromethyl-phenylpyrrolidin-2-one). The latter compound was identified by an NMR spectrum which was identical to that of the product of Step 1 above.

Step 2 Preparation of 3-(t-Butylcarbamoyl-N-methyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.

Methylamine gas was bubbled through a solution of 3-bromo-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (0.20g) from Step 1 in THF (25ml) at 0°C. After 15 minutes the reaction was allowed to warm to room temperature. After 1 hour, with methylamine still bubbling through the solution, tlc showed no remaining bromide. The solvent was evaporated in vacuo and the residue re-dissolved in dichloromethane (10ml). t-Butylisocyanate (0.22ml) and triethylamine (0.27ml) were added and the yellow solution was stirred overnight at room temperature. The solvent was then evaporated in vacuo and the residue purified by flash chromatography on silica, eluting with 50% ethyl acetate in hexane. The title compound was obtained as a colourless solid (0.185g). ^1H NMR ($CDCl_3$): δ 1.37(9H,s); 2.14(1H,m); 2.49(1H,m); 2.85(3H,s); 3.82(2H,m); 4.44(1H,brs); 5.23(1H,dd); 7.40(1H,d); 7.49(1H,t); 7.91(1H,d) overlapping 7.92(1H,s). MS m/e 357(M^+).

The procedure of this example was also used in the synthesis of Compounds 20 (m.p. 146-147°C), 36 (m.p. 132-133°C), 37 (using phenylisocyanate in

place of t-butylisocyanate), (m.p. 167-169°C), 43 (m.p. 127-128°C), 44 (m.p. 136-137°C), 52 (m.p. 135.5-136.5°C), 60 (m.p. 134-135°C), 70 (m.p. 133-135°C), 71 (m.p. 122-123°C), 124 and 282 of Table 1.

EXAMPLE 11 **Preparation of Compound 11: N-(3-Methylisoxazol-5-yl)-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetamide.**

Oxalyl chloride (0.127ml) was added to a suspension of [1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetic acid (prepared as in Example 13 below) (0.38g) in chloroform (6ml) at room temperature. Dimethylformamide (1 drop) was added, causing effervescence. After 2 hours, the reaction was cooled to 0°C and 5-amino-3-methylisoxazole (0.14g) was added, followed by triethylamine (0.36ml). The reaction darkened and a brown solid appeared. After 6 hours, the mixture was poured into ethyl acetate (100ml) and washed with sat. $NaHCO_3$ (aq) (100ml), brine (100ml) and 1N HCl (aq) (50ml) brine (100ml) and then dried (Na_2SO_4). Evaporation of the solvent in vacuo and purification of the residue by flash chromatography on silica, eluting with ethyl acetate/hexane (a gradient of 40-50% ethyl acetate) gave the crude product. Recrystallisation from ethyl acetate/hexane gave the title compound (0.14g) as a colourless solid, m.p. 182-183°C.

^1H nmr ($CDCl_3$) : 1.91-2.06(1H,m); 2.26(3H,s); 2.49-2.63(1H,m); 2.67(1H,dd); 3.01(1H,dd); 3.10-3.24(1H,m); 3.83-4.00(2H,s); 7.46(1H,br d); 7.54(1H,br t); 7.84(1H,br s), 7.92(1H,br d).

EXAMPLE 12 **Preparation of Compound 12: 2-([1-(3-trifluoromethyl) phenyl-2-pyrrolidinone-3-yl]acetylamino)-2,2-dimethylethanol**

Oxalyl chloride (0.190ml) was added to a stirred suspension of [1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetic acid (prepared as in Example 13 below) (0.570g) in chloroform (10ml) at room temperature. Dimethylformamide (1 drop) was added and stirring continued for 2 hours. The solvent was evaporated in vacuo and the residue re-dissolved in dichloromethane (20ml) and cooled to 0°C. Triethylamine (0.55ml) was added, followed by 2-amino-2,2-dimethylethanol (0.55ml) and the mixture was

stirred at 0°C for 1 hour before allowing to warm to room temperature. The reaction was diluted with ethyl acetate (100ml) and washed with water (2x50ml), brine (50ml), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica, eluting first with ethyl acetate and then with 5% methanol in ethyl acetate to give the title compound as a yellow gum. ^1H NMR ($CDCl_3$): δ 1.30(6H,s); 1.90-2.05(1H,m); 2.48(1H,dd); overlapping 2.49(1H,m); 3.04-3.15(1H,m); 3.53(1H, v broad d); 3.67(brd), 3.78-3.94(2H,m); 4.72(1H, brm); 6.44(1H,brs); 7.42(1H,d); 7.50(1H,t); 7.85-7.90(2H,m).

The procedure of this example was also used in the synthesis of Compounds 26 (m.p. 128-131°C), 27 (oil), 30 (oil) and 33 (oil) of Table 1.

EXAMPLE 13 **Preparation of Compound 13: [1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetic acid.**

Trifluoroacetic acid (1ml) was added to a solution of t-Butyl-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetate (prepared as described in Example 7) (0.70g) in dichloromethane (10ml) at room temperature. The yellow solution was stirred for 24 hours and the solvent then evaporated *in vacuo*. Trituration of the residue with ether/hexane caused a pale yellow crystalline solid to separate out. This was filtered off to give the pure title compound (0.48g),m.p. 126-128°C.
^1H NMR (d_6DMSO): δ 1.80(1H,m); 2.28(1H,m); 2.41(1H,dd); 2.74(1H,dd); 2.91(1H,m); 3.78(2H,m); 7.42(1H,d); 7.56(1H,t); 7.75(1H,d); 8.16(1H,brs).
MS m/e 287(M^+)

EXAMPLE 14 **Preparation of Compound 14: [3-(3-trifluoromethyl)phenyl -4-thiazolidinone-5-yl]acetic acid.**

Mercaptosuccinic acid (7.5g) was weighed into a 3-necked flask equipped with a Dean and Stark trap and a condensor. 3-Trifluoromethyl aniline (8.05g), toluene (100ml) and 37% aqueous formaldehyde solution (4.25ml) were introduced together with a stirrer bar. The stirred reaction mixture was slowly brought to reflux during which time all the remaining solid dissolved. Water was collected in the Dean and Stark trap once reflux was

attained, and after 15 minutes a solid began to precipitate. After 3h at reflux the hot solution was filtered through a sinter and the filtrate allowed to cool to room temperature. The solid that then precipitated was collected at the pump (7.34g) and was recrystallised from hot toluene to give the title compound (3.78g). ^{1}H NMR ($CDCl_3$/d_6DMSO): 2.95(1H,dd); 3.19(1H,dd); 4.27(1H,m); 4.82(2H,m); 7.53(2H,m); 7.71(1H,m); 7.79(1H,s). IR (Nujol mull): 3500-2500(broad), 1700cm^{-1} (broad). MS: m/e 305(M^+).

EXAMPLE 15 **Preparation of Compound 15: Ethyl [3-(3-trifluoromethyl)-phenyl-4-oxazolidinone-5-yl]acetate**

A solution of the ethyl ester of N-(3-trifluoromethylphenyl) fumaric acid amide (10.0g) in DMF (50ml) was added to a stirred suspension of sodium hydride (0.14g of a 60% oil dispersion) in DMF (25ml). The reaction mixture turned bright orange. Paraformaldehyde (5.80g) was then added in one portion. The reaction turned brown. After 15 minutes, the reaction was poured into water (250ml) with approximately 10ml of 2N HCl (aq). The aqueous mixture was extracted with ether (2x200ml). The combined organic extracts were washed with brine and then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the oxazolidinone as a brown oil (10.858g, 98%) which solidified on standing. The procedure of this example was also used in the preparation of Compounds 45, 62 242 and 243 of Table I.

EXAMPLE 16 **Preparation of Compound 17 and Compound 18: N-(1,1-dimethyl-propyl)-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetamide and N-(1,1-dimethylprop-2-enyl)-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl] acetamide.**

The propargyl amide (Compound 16, prepared by a method similar to that described in Example 8) (0.407g) was dissolved in ethyl acetate (20ml). 5% Palladium on calcium carbonate, poisoned with lead (0.04g) in ethyl acetate (5ml) was added. With stirring, the flask was evacuated and flushed with hydrogen via a balloon. This procedure was repeated twice. After 2 hours hydrogenation at one atmosphere, the reaction was filtered through a pad of Hyflo^{TM} to remove catalyst. Evaporation of the filtrate gave a solid which

was purified by HPLC, eluting with 25% acetone in hexane to give firstly Compound 17 as a colourless solid (0.095g), m.p 117°C; and then Compound 18 as a colourless solid (0.159g), m.p. 111°C. This procedure was also used in the preparation of Compound 34 (m.p. 104-105°C), Compound 35 (m.p. 120-121°C), Compound 46, Compound 47, Compound 48, Compound 49, Compound 56 (m.p. 98-99°C), Compound 57 (m.p. 171-172°C), Compound 74 (m.p. 77-81°C), Compound 79, Compound 80 (m.p. 83-84.5°C), Compound 98 (m.p. 111.5-112.5°C), Compound 118 (m.p. 114.5-116°C), Compound 240, Compound 255 and Compounds 273-277 of Table I.

EXAMPLE 17 **Preparation of Compounds 40 and 39: N-(1,1-dimethylpropynyl)-[1-(3-trifluoromethyl)phenyl-3-oxazolidinone-5-yl]acetamide and N-(1,1-dimethylpropynyl)-[1-(3-trichloromethyl)phenyl-3-oxazolidinone-5-yl] acetamide**

The ester (Compound 15, prepared as in Example 15) (0.8g) was dissolved in dry dichloromethane (20ml) and aluminium trichloride (0.84g) added. To this suspension was added dropwise 1,1-dimethylpropargylamine (1.16g). When the effervescence had ceased and exotherm of 15°C died down, the mixture was stirred at room temperature for 1 hour. The mixture was then carefully quenched with 2M HCl(aq), the layers separated and the aqueous layer extracted with dichloromethane. The combined organics were washed with water, dried over $MgSO_4$ and evaporated. The solid was recrystallised and the crystallisation residue purified by HPLC and then preparative TLC to give Compound 39 as a white solid (0.168g) and Compound 40 as a white solid (0.08g). This procedure was also used in the preparation of Compounds 21, 50, 66, 67 and 68 of Table I.

EXAMPLE 18 **Preparation of Compound 24: N-cyclobutyl-[1-(3-trifluoromethyl)phenyl-2-pyrrolidinone-3-yl]acetamide.**

The acid chloride (prepared as described in Example 8 from the corresponding acid, Compound 13, 0.5g) was dissolved in dichloromethane (18ml). Sodium carbonate (0.463g) was dissolved in water (18ml) and added to cyclobutylamine hydrochloride (0.207g). After the effervescence had subsided, this solution was added to the acid chloride. After vigorous

stirring, the reaction was left to stand overnight. The reaction was diluted with dichloromethane (20ml) and washed with $NaHCO_3$ (aq). The aqueous layer was re-extracted with dichloromethane and then with brine before drying over $MgSO_4$. Evaporation gave a yellow oil which was purified by column chromatography, eluting with 90% ethyl acetate in hexane to give Compound 24 as a white solid (0.475g), m.p. 146-147°C. This procedure was also used for the preparation of Compound 25 of Table I (m.p. 96.5-99°C).

EXAMPLE 19 **Preparation of Compound 32:N-t-Butyl-2-[1-(3-trifluoromethyl phenyl)-2-pyrrolidinone-3-yl]propamide**

Step 1 Preparation of t-butyl 2-[1-(3-trifluoromethylphenyl)-2-pyrrolidinone-3-yl] propanoate

The ester (Compound 7, 2.112g) was dissolved in THF (30ml) at -78°C. Lithium hexamethyldisilazide (6.79ml of a 1.0m THF solution) was added via syringe. After 30 minutes at -78°C, iodomethane (1.752g) was added. This was left to stir at -78°C for 20 minutes and then allowed to warm to room temperature. After 10 minutes at room temperature, the reaction was poured into water (30ml). The aqueous layer was re-extracted with ether (x2) and the combined organic layers were washed with sodium thiosulphate solution and dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography, eluting with 25% ethyl acetate in hexane to give a (1:1) mixture of the required product and the 3-methylpyrrolidone product (1.0g).

Step 2

The mixture of two esters obtained in Step 1 was hydrolysed according to the method in Example 13, to give a mixture of the corresponding acids (0.707g).

Step 3

The mixture of acids obtained in Step 2 was reacted with oxalyl chloride and then t-butylamine as in the method for Example 10. The mixture of amide products was separated by HPLC to give the title compound as a white solid (0.208g), m.p. 107.5-111°C.

EXAMPLE 20 **Preparation of Compound 41: 3-(t-Butylcarbamoylthio)-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

Step 1

To a solution of thioacetic acid (0.0493g) in ether (5mls) at 0°C under nitrogen atmosphere was added triethylamine (0.0656g) dropwise. The bromo-pyrrolidinone (prepared as in Step 1 of Example 10), (0.2g) in ether (3ml) was added. The mixture was allowed to warm to room temperature and then heated to reflux for 4 hours. The mixture was diluted with ether, washed with 2M HCl(aq) solution (x3), water (x2), brine and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography, eluting with ethyl acetate in hexane (27:73) to give the thioacetate (0.211g).

Step 2

The thioacetate, prepared as in Step 1 (0.03g) was dissolved in methanol and cooled to 0°C. Ammonia gas was bubbled through the mixture for 15 minutes. The mixture was concentrated to dryness. Chromatography, eluting with ethyl acetate/hexane (25:75) gave the thiol compound.

Step 3

The thiol compound obtained in Step 2 was reacted with t-Butylisocyanate according to Example 10 to give the thiocarbamate compound 41 as a colourless solid, m.p. 104-106°C. A similar procedure was used to prepare Compounds 42 (m.p. 119-120°C), 75 (m.p. 111-112.5°C), 76 (m.p. 83-86°C), 127, 309, 314, 319, 320, 323 and 327 of Table 1.

EXAMPLE 21 **Preparation of Compound 61: 3-(t-Butyloxycarbonyl-N-methyl)-amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

To a solution of Compound 10 (0.40g) prepared as in Example 10 in dioxane/water (1:1,6ml) was added triethylamine (0.32ml) and then Boc-on. The reaction was left at room temperature overnight and then partitioned between ethyl acetate/water. The aqueous layer was re-extracted with ethyl acetate and the organics washed with water (x2), 0.5N NaOH (aq), water and brine and then dried (Na_2SO_4). Evaporation and chromatography, eluting

with ethyl acetate/hexane (30:70) to give the carbamate, Compound 61, as a colourless solid (0.515g), m.p. 135-136°C.

A similar procedure was used to prepare Compounds 58 (m.p. 106-107°C), 59 (m.p. 136-137°C), 69 (m.p. 147-148°C) and 73 (m.p. 139-140°C) of Table 1.

EXAMPLE 22 **Preparation of Compound 77: 3-(t-Butyloxycarbonyloxy)-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone**

t-Butyloxycarbonyl anhydride (Boc-anhydride) (0.48ml) was added to a solution of the hydroxy pyrrolidinone (prepared as in step 1 or 1a of Example 9 (0.50g) in dichloromethane (10ml), followed by DMAP (0.024g). After 10 minutes, effervescence started. The solvent was evaporated to half volume after 1½ hours and the residue purified by chromatography, eluting with 20% ethyl acetate/hexane to give the carbamate 77 as a colourless solid (0.62g), m.p. 80-92°C. This procedure was also used for the preparation of Compound 81 of Table I (m.p. 105-108°C).

EXAMPLE 23 **Preparation of Compound 99 : 3-(t-Butylcarbamoyl-N-ethoxycarbonylmethylamino)-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

Step 1 Preparation of 3-(N-ethoxycarbonylmethyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.

Ethylbromoacetate (0.155ml) was added via syringe to a solution of 3-amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (prepared by a similar method to that described in Example 1, Step 4) (0.31g) and triethylamine (0.176ml) in THF (5ml) at room temperature. After 16 hours, the mixture was poured into saturated $NaHCO_3$(aq) and extracted with ethyl acetate (x2). Combined extracts were dried (Na_2SO_4), evaporated and the residue purified by flash chromatography (eluting with ethyl acetate) to give 3-(N-ethoxycarbonylmethyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone as a colourless solid (0.315g).

Step 2 Preparation of 3-(t-Butylcarbamoyl-N-ethoxycarbonyl-methyl)-amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.

3-(N-Ethoxycarbonylmethyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolid

inone (0.215g) (prepared as described in Step 1) was dissolved in dichloromethane (3ml). Triethylamine (0.5ml) and t-Butylisocyanate (0.25ml) were added and the reaction left at room temperature for 16 hours. After this time, the solvent was evaporated, the residue purified by flash chromatography (eluting with ethyl acetate) to give the crude product. This was recrystallised from ethyl acetate/hexane to give the pure title compound (0.13g) as colourless crystals, m.p. 144-146°C.
A similar procedure was used to prepare Compound 119 (m.p. 130.5-132.5°C).

EXAMPLE 24 **Preparation of Compound 86: 3-(t-Butylcarbamoyl-N-methoxy)-amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

Step 1 Preparation of 3-(N-methoxy)amino-1-(3-trifluoromethyl)phenyl-2--pyrrolidinone.

Methoxylamine hydrochloride (3.39g) and sodium carbonate (4.29g) were stirred together in methanol (20ml) for 5 minutes. This mixture was then added to a solution of 3-bromo-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (2.5g) (prepared as described in Example 10, Step 1) in methanol (30 ml) at room temperature. The mixture was heated to reflux overnight. Further methoxylamine hydrochloride (3.39g) was added and heating continued for a further 24 hours. After cooling, the reaction was poured into water and extracted with dichloromethane (x3). The combined extracts were washed with brine and dried (Na_2SO_4). Chromatography (eluting with 40% ethyl acetate/hexane) gave the product as a pale yellow oil which crystallised. This proved to be a 4:1 mixture of the title compound and the corresponding 3-hydroxyl-(3-trifluoromethyl)phenyl-2-pyrrolidinone (0.068g) and was used directly in the next step.

Step 2 Preparation of 3-(t-Butylcarbamoyl-N-methoxy)amino-1--(3-trifluoromethyl)phenyl-2-pyrrolidinone.

A solution of 3-(N-methoxy)amino-1-(3-trifluoromethyl)phenyl-2--pyrrolidinone (0.4g) (prepared as described in Step 1), triethylamine (0.5ml) and t-butylisocyanate (0.5ml) in dichloromethane (1ml) was stirred at room temperature for 20 hours. After this time, further quantities of

triethylamine (0.25ml) and t-butylisocyanate (0.25ml) were added and stirring continued for 3 hours. The solvent was evaporated and the product purified by flash chromatography, eluting with 40-50% ethyl acetate in hexane. The product was obtained as a brown oil which crystallised to give the title compound (0.275g), m.p. 127.5-128.5°C.

A similar procedure was used to prepared Compound 88 (m.p. 102-104°C).

EXAMPLE 25 **Preparation of Compound 123: 3-(3,3-dimethylbutanoyl-N-formyl)-amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone.**

Step 1 Preparation of 3-methylsulfonyloxy-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone.

3-Hydroxy-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone (5.22g) (prepared by a similar procedure to that described in Step 1 or Step 1a of Example 9) was dissolved in CH_2Cl_2 (75ml) and cooled to 5°C. Triethylamine (3.48ml) was added followed by dropwise addition of methane sulfonyl chloride (1.64ml) over 15 minutes. The reaction was left to stir for 20 minutes at 5°C and then allowed to warm to room temperature and stirred for 2 hours. After diluting with CH_2Cl_2, the mixture was washed with water (x2) and dried over $MgSO_4$. Concentration gave 6.63g of the mesylate as a pale brown solid.

Step 2 Preparation of 3-(N-formyl)amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone.

Sodium hydride (0.33g of an 80% oil dispersion, washed with 40-60 petrol) was suspended in dry DMF (2ml). Formamide (10ml) was added dropwise over 15 min, with ice bath cooling. The mesylate (prepared as in Step 1) (3.39g) was added in DMF (15ml) over 10 min at 20°C and the resulting dark yellow solution heated to 50°c for 3 hours. After cooling, the reaction was added to water and extracted with ethyl acetate (x3). The combined extracts were washed with water (x3), dried over $MgSO_4$, concentrated and triturated with ether/petrol to give the N-formyl compound as a pink solid (0.97g).

Step 3 Preparation of 3-(3,3-dimethylbutanoyl-N-formyl)amino-1-1(3-trifluoromethoxy)phenyl-2-pyrrolidinone.

The N-formyl compound (prepared as in Step 2) (0.97g) was dissolved in CH_2Cl_2 (20ml). triethylamine (0.51ml) was added, followed by 3,3-dimethylbutanoyl chloride (0.51ml) in CH_2Cl_2 (5ml) which was added dropwise over 5 min. The reaction was stirred at room temperature for 17 hours, whereupon further triethylamine (0.25ml) and 3,3-dimethylbutanoyl chloride (0.25ml) were added. After a further 3 hours, the reaction was diluted with CH_2Cl_2 and washed with water. After drying over $MgSO_4$, the solvent was evaporated to give the crude product as an orange oil. Chromatography, eluting with ether gave a pale yellow product which was triturated with ether/petrol to give the title compound as a white solid (0.57g).

EXAMPLE 26 **Preparation of Compound 94: 3-(t-Butylthiocarbamoyl-N-methyl)-amino-1-(3-difluoromethoxy)phenyl-2-pyrrolidinone.**

3-(N-methyl)amino-1-(3-difluoromethoxy)phenyl-2-pyrrolidinone (0.20g) (prepared in a similar procedure to that described in Step 2 of Example 9) was dissolved in CH_2Cl_2 (5ml). t-Butyl isothiocyanate (0.13ml) and triethylamine (0.16ml) were added and the reaction stirred at room temperature overnight. The solvent was evaporated and the residue purified by column chromatography, eluting with 60% ethyl acetate/hexane to give the thiourea title compound as a colourless solid (0.253g), m.p. 141-143°C. A similar procedure was used to prepared Compounds 95 (m.p. 141-144°C), 100 (m.p. 140-142°C), 107 (m.p. 100-107°C), 109 (m.p. 148.5-150°C), 112 (m.p. 130-132°C), 114 (m.p. 108-109°C) and 115 (m.p. 142-143°C).

EXAMPLE 27 **Preparation of Compound 93: 3-(t-Butylcarbamoyl-N-allyl)-amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone.**

Step 1 Preparation of 3-(N-allyl)amino-1-(3-trifluoromethoxy)-phenyl-2-pyrrolidinone.

3-Bromo-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone (0.80g) (prepared by a method similar to that described in Example 10, Step 1) was dissolved in THF. To this solution was added allylamine (0.70g) and the mixture stirred at room temperature for 4 hours and then left to stand overnight. The reaction was diluted with ethyl acetate, washed with water (x3), brine and dried over $MgSO_4$. Filtration and evaporation of the solvent gave a crude product that was purified by column chromatography (eluting with 90-100% ethyl acetate in hexane) to give the pure N-allyl compound (0.68g).

Step 2 Preparation of 3-(t-Butylcarbamoyl-N-allyl)amino-1-(3-trifluoro-methoxy)phenyl-2-pyrrolidinone.

The N-allyl derivative (0.23g) (prepared as described in Step 1) was dissolved in CH_2Cl_2 (3ml) and treated with triethylamine (0.16ml) followed by t-butylisocyanate (0.22ml). After 48 hours at room temperature, the reaction was diluted with CH_2Cl_2, washed with 2N HCl (aq) (x2), brine and dried over $MgSO_4$. The mixture was filtered and concentrated and the residue purified by flash chromatography, eluting with 40% ethyl acetate in hexane. The urea title compound was obtained as colourless solid (0.293g), m.p. 107-108°C.

A similar procedure was used to prepare Compounds 19 (m.p. 112-114°C), 38 (m.p. 157-158°C), 64 (108.5-110°C), 65 (m.p. 146-148°C), 78 (m.p. 110-111.5 °C), 82 (m.p. 136.5-138.5°C), 83 (gum), 84 (m.p. 111-112°C), 85 (m.p.137-138°C), 87, 90 (m.p. 95-96.5°C), 91 (m.p. 136.5-137.5°C), 92 (solid gum), 93 (m.p. 107-108°C) 101 (m.p. 111.5-112.5°C), 105 (m.p. 137-138.5°C), 106 (m.p. 84-87°C), 108 (m.p. 107-109°C), 111, 116 (m.p. 172-173.5°C), 120 (m.p. 105-107.5°C), 121 (m.p. 117-118.5°C), 122 (m.p. 106-107.5°C), 241, 242, 254, 312, 316, 317 and 318 of Table I.

EXAMPLE 28 **Preparation of Compound 117: 3-(t-Butylcarbamoyl-N-acetoxy-ethyl)amino-1-(3-trifluoromethyl)phenyl -2-pyrrolidinone**

Compound 82 (0.25g) (prepared by a similar method to that described in Example 27) was dissolved in CH_2Cl_2 (5ml). To this was added triethylamine (0.091ml) followed by acetyl chloride (0.046ml). The reaction was stirred at room temperature for 45 minutes, diluted with CH_2Cl_2 and washed with 2N HCl (aq) (x2), brine and dried over $MgSO_4$. Filtration and evaporation gave the crude product which was purified by column chromatography, eluting with ethyl acetate in hexane (1:1). The acetoxy compound was obtained as a colourless solid, m.p. 129-131°C.

EXAMPLE 29 **Preparation of Compound 128:**

Compound 99 (prepared as described in Example 23) (0.110g) was dissolved in THF (5ml) and sodium hydride (30mg of a 60% oil dispersion) added. The reaction effervesced and turned yellow, then pinkish orange. After 4 hours, the mixture was poured into water and extracted with ethyl acetate (x3). The combined extracts were dried ($MgSO_4$) and evaporated. Purification by flash chromatography (eluting with ethyl acetate) gave the cyclic compound 128 as a pale yellow gum (0.076g).

EXAMPLE 30 **Preparation of Compound 129**

To an ice-cooled solution of Compound 55 (prepared by a similar procedure to that described in Example 1) (0.100g) in toluene (5ml) was added oxalyl chloride (0.027ml). The mixture was removed from the ice-bath and stirred at room temperature for ½ hour and then 80°C for 1 hour. The solvent was evaporated to give the cyclic compound 129.

A similar procedure was also used to prepare Compound 133.

EXAMPLE 31 **Preparation of Compound 130**

Compound 101 (prepared by a similar procedure so that described in Example 27) (0.100g) was dissolved in THF (2ml) and 2N HCl (2ml) added. The reaction was stirred at room temperature overnight. The mixture was poured

into ethyl acetate. The organic phase was separated, dried ($MgSO_4$) and evaporated to give Compound 130 as a colourless solid.

EXAMPLE 32 **Preparation of Compound 131**

Compound 28 (prepared by a similar method to that described in Example 1) (0.100g) was dissolved in toluene ($10cm^3$). Glyoxal. $3H_2O$ (0.033g) and PTSA (catalytic amount) were added and the mixture heated under Dean and Stark conditions for 4 hours. Further glyoxal. $3H_2O$ (0.033g) was added and the mixture heated under reflux for a further 4 hours. After evaporation of the solvent, the residue was purified by chromatography, eluting with ethyl acetate in hexane (1:2) to give Compound 131 as a colourless solid (0.043g).

EXAMPLE 33 **Preparation of Compound 132**

Compound 28 (prepared by a similar method so that described in Example 1) (0.115g) was dissolved in toluene (10ml). Paraformaldehyde (0.023g) and PTSA (catalytic amount) were added and the mixture heated under Dean and Stark conditions for 8 hours. Additional paraformaldehyde (0.023g) was added at 2 hour intervals over this time. The mixture was allowed to cool and the solvent evaporated. The residue was purified by chromatography (eluting with ethyl acetate/hexane 1:2) to give Compound 132 (0.018g).

A similar procedure was also used to prepare Compound 134.

EXAMPLE 34 **Preparation of Compound 135: 5-t-Butylcarbamoyloxy-3(3-trifluoromethylphenyl)oxazolidin-4-one**

Step 1 Preparation of benzyl dibenzyloxyacetate

A solution of dichloroacetic acid (12.89g) in benzyl alcohol (50ml) was added to a solution of sodium benzyloxide, from sodium hydride (13.53g, 55% dispersion in mineral oil) in benzyl alcohol (150ml). The resultant mixture was heated at 190°C for four hours, then the solvent distilled off

under reduced pressure. The residue was triturated with ether, the solid removed by filtration and distributed between hydrochloric acid (2N) and ether. The extracts were dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane as eluant, to give benzyl dibenzyloxyacetate (12.50g) as a colourless oil. None of the expected corresponding acid was eluted with more polar solvents.

NMR ($CDCl_3$): δ 4.7(4H,dd), 5.1(1H,s), 5.2(2H,s), 7.3(15H,m). MS: M^+ 362.

NB When the residue was triturated with ether, it appears that some of the ester product may have been lost; the work-up procedure should be modified in view of ester, rather than acid, being produced.

Step 2 Preparation of dibenzyloxyacetic acid

Water (20ml) and potassium carbonate (10.64g) were added to a solution of benzyl dibenzyloxyacetate (11.15g), from Step 1 above, in tetrahydrofuran (80ml) and the mixture heated under reflux for twenty-four hours. It was allowed to cool, poured into water, extracted with ether, acidified with concentrated hydrochloric acid and again extracted with ether. The extract from acidic solution was washed with brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (8.12g), used crude in Step 3.

NMR ($CDCl_3$): δ 4.7(4H,m), 5.1(1H,bs), 7.3(10H,m), 9.2(1H,bs).

Step 3 Preparation of 2,2-dibenzyloxy-N(3-trifluoromethylphenyl)acetamide

A stirred solution of dibenzyloxyacetic acid (4.0g), from Step 2, in dichloromethane (40ml) was cooled to 0°C and treated dropwise with, successively, N,N-dimethylformamide (100mg) and oxalyl chloride (2.0g). After thirty minutes, pyridine (3.52g), 3-trifluoromethylaniline (2.64g) and 4-dimethylaminopyridine (100mg) were added. The mixture was stirred at 0°C for a further thirty minutes, then allowed to warm to room temperature. After three hours, it was poured into water, extracted with ethyl acetate and the extracts washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate solution, and brine. After drying over magnesium sulphate, the extracts were evaporated under reduced pressure to

give the title compound (5.62g) as an orange gum, sufficiently pure to be used in Step 4.
NMR ($CDCl_3$): δ 4.7(4H,dd), 5.1(1H,s), 7.3(12H,m), 7.8(1H,dd), 7.85(1H,s), 8.5(1H,bs).

Step 4 Preparation of 2,2-dibenzyloxy-N-benzyloxymethyl-N(3-trifluoromethylphenyl)acetamide

2,2-Dibenzyloxy-N(3-trifluoromethylphenyl)acetamide, (4.75g), from Step 3, benzyl chloromethylether (1.79g) and tetrabutylammonium iodide (100mg) were added successively to a vigorously stirred mixture of aqueous sodium hydroxide solution (100ml, 50%) and dichloromethane (100ml). After stirring for eighteen hours, the mixture was extracted several times with dichloromethane and the extracts washed with brine. After drying over magnesium sulphate, the extracts were evaporated under reduced pressure. The residue was chromatographed on silica, using hexane-ethyl acetate (4:1) as eluant, to give the title compound (2.87g).
NMR ($CDCl_3$): δ 4.6(6H,m), 4.9(1H,bs), 5.15(2H,bs), 7.3(18H,m), 7.55(1H,dd).

Step 5 Preparation of 5-hydroxy-3(3-trifluoromethylphenyl)oxazolidin-4-one

A mixture of 2,2-dibenzyloxy-N-benzyloxymethyl-N(3-trifluoromethylphenyl)acetamide (0.27g), prepared as described in Step 4, 10% palladium on carbon (50mg), trifluoroacetic acid (1ml) and dichloromethane (50ml) was stirred under an atmosphere of hydrogen for five hours. It was filtered through Hyflo Supercel ™, evaporated under reduced pressure and chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give the title compound (0.07g) as a waxy solid, m.p. 75-76°C.
NMR ($CDCl_3$): δ 5.35(1H,bs), 5.45(1H,d), 5.7(2H,m), 7.5(2H,m), 7.65(1H,d), 7.7(1H,s).

Step 6 Preparation of 5-t-Butylcarbamoyloxy-3(3-trifluoromethylphenyl)oxazolidin-4-one

A stirred solution of 5-hydroxy-3(3-trifluoromethylphenyl)-oxazolidin-4-one, prepared as described in Step 5, can be converted into the Title compound, by treatment with t-butyl isocyanate in the presence of triethylamine as described in Step 5 of Example 1.

EXAMPLE 35 **Preparation of Compound 136: 5-t-Butylcarbamoyloxy-3(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one

A stirred solution of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.0g) in toluene (50ml) was treated successively with thioglycolic acid (2.77g), 37% aqueous formaldehyde solution (2.45ml) and p-toluenesulphonic acid (0.025g). The reaction mixture was heated under reflux, water being collected in a Dean and Stark apparatus. After four hours it was cooled, washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (4.35g, m.p. 99-100°C). NMR ($CDCl_3$): δ 3.9(2H,s); 5.25(2H,s). MS: M^+ 255.

Step 2 Preparation of 5-chloro-3(5-trifluoromethyl-1,3,4-thiadiazol--2-yl)thiazolidin-4-one

Sulphuryl chloride (0.27ml) was added dropwise to a stirred solution of 3(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one (0.5g), prepared as described in Step 1 above, in dichloromethane (20ml), cooled in an ice-salt bath. The mixture was stirred for a further two hours, then allowed to warm to room temperature over one hour. It was then evaporated under reduced pressure and the residue chromatographed on silica, using hexane-ethyl acetate (3:1) as eluant, to give the title compound (0.34g) as a white solid. NMR ($CDCl_3$): δ 5.4(2H,s); 5.9(1H,s).

Step 3 Preparation of 5-hydroxy-3(5-trifluoromethyl-1,3,4-thiadiazol--2-yl)thiazolidin-4-one

A solution of 5-chloro-3(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one (1.72g), prepared as described in Step 2 above, in tetrahydrofuran (20ml) was added dropwise to a vigorously stirred aqueous

solution of potassium dihydrogen phosphate buffer (20ml, to retain pH 4.5). The reaction mixture was stirred for twenty hours at room temperature, allowed to stand overnight and diluted with water. The white precipitate was filtered off and dried in vacuo to give the title compound (1.31g, m.p. 176-177°C). NMR (DMSO-d_6): δ 5.15 (2H,dd); 5.9(1H,d); 7.4(1H,d). MS: M^+ 271.

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one

A stirred solution of 5-hydroxy-3(5-trifluoromethyl-1,3,4-thiadiazol--2-yl)thiazolidin-4-one (0.91g), from Step 3, in dichloromethane (25ml) was cooled in ice and treated successively with t-butyl isocyanate (0.37g), dropwise, and triethylamine (0.37g). The mixture was allowed to warm, stirred for eighteen hours at room temperature, then evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine, dried over magnesium sulphate and evaporated under reduced pressure. Chromatography on silica, using hexane-diethyl ether (3:1) as eluant, gave the title compound (0.94g, m.p. 151-152°C). NMR ($CDCl_3$): δ 1.3(9H,s); 4.85(1H,bs); 5.3(2H,m); 6.3(1H,s). MS: MH^+ 371.

EXAMPLE 36 **Preparation of Compound 137: 5-t-Butylcarbamoyloxy-3(5-methyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(5-methyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one

By a procedure similar to that described in Step 1 of Example 35, but using 2-amino-5-methyl-1,3,4-thiadiazole (5.0g), thioglycolic acid (4.0g), 37% aqueous formaldehyde solution (3.52ml), p-toluenesulphonic acid (0.025g) and toluene (60ml). The toluene layer was decanted and evaporated under reduced pressure to give the title compound (6.04g, m.p. 139-140°C). NMR ($CDCl_3$): δ 2.7(3H,s); 3.8(2H,s); 5.15(2H,s). MS: M^+ 201.

Step 2 Preparation of 5-hydroxy-3(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one

N-chlorosuccinimide (2.84g) was added portionwise to a stirred solution of

3(5-methyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one (4.27g), prepared as described in Step 1 above, in dichloromethane (30ml). After twenty hours, the solvent was removed under reduced pressure. The residue was converted into the title compound by treatment with aqueous potassium dihydrogen phosphate solution in tetrahydrofuran by a procedure similar to that described in Example 35, Step 3. The reaction mixture was diluted with water and extracted with ethyl acetate. The extracts were washed, dried over magnesium sulphate, evaporated under reduced pressure and chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give the title compound (1.47g, m.p. 154-156°C). NMR (DMSO-d_6): δ 2.6(3H,s); 5.0(2H,m); 5.75(1H,bd); 7.25(1H,bd). MS: M^+ 217.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(5-methyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 5-hydroxy-3(5-methyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-one (0.5g), from Step 2, t-butyl isocyanate (0.25g), triethylamine (0.26g) and dichloromethane (15ml). Chromatography on silica, using dichloromethane-ethanol (49:1) as eluant, gave the title compound (0.32g, m.p. 160-161°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.75(3H,s); 4.85(1H,bs); 5.2(2H,m); 6.3(1H,s). MS: MH^+ 317.

EXAMPLE 37 **Preparation of Compound 138: 5-t-Butylcarbamoyloxy-3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one

By a procedure similar to that described in Step 1 of Example 35, but using 2-amino-6-trifluoromethylpyridine (5.0g), thioglycolic acid (3.1g), 37% aqueous formaldehyde solution (2.7ml), p-toluenesulphonic acid (0.025g) and toluene (50ml). The crude product (5.76g, m.p. 87-88°C) was sufficiently pure for use in Step 2. NMR ($CDCl_3$): δ 3.8(2H,s); 5.15(2H,s); 7.5 (1H,d); 7.9(1H,t); 8.55(1H,d). MS: M^+ 248.

Step 2 Preparation of 5-chloro-3(6-trifluoromethylpyridin-2-yl)-thiazolidin-4-one

A stirred solution of 3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one (4.75g), prepared as described in Step 1 above, in dichloromethane (100ml) was cooled to 0°C and treated dropwise with sulphuryl chloride (1.29g). After one hour, the mixture was allowed to warm to room temperature and stirred for a further three hours. It was then again cooled to 0°C and treated dropwise with more sulphuryl chloride (1.29g). After thirty minutes, the mixture was evaporated under reduced pressure and the residue chromatographed on silica, using hexane-ethyl acetate (3:1) as eluant, to give the title compound (3.03g) used directly in the following step. NMR ($CDCl_3$): δ 5.3(2H,m); 5.8(1H,s); 7.5(1H,d); 7.95(1H,t); 8.6(1H,d).

Step 3 Preparation of 5-hydroxy-3(6-trifluoromethylpyridin-2-yl)-thiazolidin-4-one

5-Chloro-3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one (3.03g), prepared as described in Step 2 above, was hydrolysed using aqueous potassium dihydrogen phosphate solution in tetrahydrofuran by a procedure similar to that described in Example 36, Step 2. The crude product (2.58g, m.p. 120°C) was sufficiently pure for use in Step 4 and Example 38. NMR ($CDCl_3$): δ 3.5(1H, very broad), 5.2(2H,m); 5.75(1H,bs); 7.5(1H,d); 7.95(1H,t); 8.6(1H,d). MS: MH^+ 265.

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(6-trifluoromethylpyridin-2-yl) thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 5-hydroxy-3(6-trifluoromethylpyridin-2-yl) thiazolidin-4-one (1.0g), from Step 3, t-butyl isocyanate (0.41g), triethylamine (0.42g) and dichloromethane (30ml). Chromatography on silica, using hexane-ethyl acetate (3:1) as eluant, gave the title compound (1.02g, m.p. 118°C). NMR ($CDCl_3$): δ 1.3(9H,s); 4.8(1H,bs); 5.2(2H,s); 6.3(1H,s); 7.5(1H,d); 7.95(1H,t); 8.65(1H,d). MS: MH^+ 364.

EXAMPLE 38 **Preparation of Compound 139: 5-N(1,1-dimethylprop-2-ynyl)-carbamoyloxy-3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 1,1-dimethylprop-2-ynyl isocyanate

A stirred solution of 1-amino-1,1-dimethylpropyne (14.30g) in toluene (25ml) was cooled to 0°C and solutions of phosgene in toluene (1.93M, 88.3ml) and sodium hydroxide (13.70g) in water (50ml) were added simultaneously over twenty minutes. The resultant suspension was stirred for a further five minutes, then filtered through phase-separating paper. The filtrate, a toluene solution containing the title compound (2240cm^{-1}), was used directly in subsequent reactions.

Step 2 Preparation of 5-N(1,1-dimethylprop-2-ynyl)carbamoyloxy-3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 5-hydroxy-3(6-trifluoromethylpyridin-2-yl) thiazolidin-4-one (1.38g), prepared as described in Example 37, Steps 1-3, 1,1-dimethylprop-2-ynyl isocyanate (14.38ml, solution in toluene), from Step 1, triethylamine (0.58g) and dichloromethane (30ml). Chromatography on silica gel, using hexane-ethyl acetate (3:1) as eluant, gave the title compound (1.39g, m.p. 85-86°C). NMR ($CDCl_3$): δ 1.6(6H,s); 2.35(1H,s); 5.15(1H,bs); 5.2(2H,s); 6.3(1H,s); 7.5(1H,d); 7.95(1H,t); 8.6(1H,d). MS: MH^+ 374.

EXAMPLE 39 **Preparation of Compound 140: 5-N(1,1-dimethylprop-2-enyl) carbamoyloxy-3(6-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

A solution of 5-N(1,1-dimethylprop-2-ynyl)carbamoyloxy-3(6-trifluoro-methylpyridin-2-yl)thiazolidin-4-one (0.5g), prepared as described in Example 38, in dichloromethane (10ml) was hydrogenated over 5% palladium on carbon catalyst (0.05g). After nine hours, the mixture was filtered and the filtrate evaporated under reduced pressure. The residue was

chromatographed on silica, using hexane-ethyl acetate (3:1) as eluant, to give the title compound (0.42g) as a colourless gum. NMR ($CDCl_3$): δ 1.4(6H,s); 4.95(1H,bs); 5.1(2H,m); 5.2(2H,s); 5.95(1H,dd); 6.3(1H,s); 7.5(1H,d); 7.95(1H,t); 8.6(1H,d). MS: MH^+ 376.

EXAMPLE 40 **Preparation of Compound 141: 3(4,6-Bis-trifluoromethylpyridin-2-yl)-5-t-butylcarbamoyloxy-thiazolidin-4-one**

Step 1 Preparation of 3(4,6-Bis-trifluoromethylpyridine-2-yl) thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Step 1 of Example 35, but using 2-amino-4,6-bis-trifluoromethylpyridine (5.0g), thioglycolic acid (2.0g), 37% aqueous formaldehyde solution (1.8ml), p-toluenesulphonic acid (0.025g) and toluene (50ml). The crude product (4.32g), isolated as a viscous orange oil which solidified on standing, was sufficiently pure for use in Step 2. NMR ($CDCl_3$): δ 3.8(2H,s); 5.15(2H,s); 7.65(1H,s); 8.9(1H,s). MS: M^+ 316.

Step 2 Preparation of 3(4,6-bis-trifluoromethylpyridin-2-yl) -5-hydroxythiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 37, Steps 2 and 3, but using 3(4,6-bis-trifluoromethylpyridin-2-yl) thiazolidin-4-one (3.53g), prepared as described in Step 1 above, sulphuryl chloride (0.46ml and 0.4ml) and dichloromethane (30ml). The reaction mixture was evaporated under reduced pressure to give a mixture (3.93g) of the desired 5-chloro derivative, the 5,5-dichloro analogue and hydrolysis products. NMR ($CDCl_3$): δ for the 5-chloro compound only: δ 5.35(2H,m); 5.8(1H,s); 7.7(1H,s); 8.9(1H,s). A solution of the mixture (3.93g) in tetrahydrofuran was hydrolysed in a manner similar to that described in Example 36, Step 2. The crude product was chromatographed on silica, using hexane-ethyl acetate (3:1) as eluant, to give the title compound (0.39g, m.p. 99-101°C). NMR ($CDCl_3$): δ 3.5(1H,d); 5.2(2H,m); 5.75(1H,d); 7.7(1H,s); 9.0(1H,s).

Step 3 Preparation of 3(4,6-Bis-trifluoromethylpyridin-2-yl)-5-t-butyl-carbamoyloxy-thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 3(4,6-bis-trifluoromethylpyridin-2-yl)-5-hydroxythiazolidin-4-one (0.36g), from Step 2, t-butyl isocyanate (0.12g), triethylamine (0.12g) and dichloromethane (20ml). Chromatography on silica gel, using hexane-ethyl acetate (4:1) as eluant, gave the title compound (0.30g) as a pale yellow gum. NMR ($CDCl_3$): δ 1.35 (9H,s); 4.8(1H,bs); 5.2(2H,s); 6.3(1H,s); 7.7(1H,s); 9.0(1H,s). MS: MH^+ 432.

EXAMPLE 41 **Preparation of Compound 142: 5-t-Butylcarbamoyloxy-3(5-trifluoromethylpyridin-3-yl)thiazolidin-4-one**

Step 1 Preparation of 3(5-trifluoromethylpyridin-3-yl)thiazolidin-4-one.

The title compound was prepared by a procedure similar to that described in Step 1 of Example 35, but using 3-amino-5-trifluoromethylpyridine (5.0g), thioglycolic acid (3.1g), 37% aqueous formaldehyde solution (2.7ml), p-toluenesulphonic acid (0.025g) and toluene (50ml). The toluene layer was decanted, washed with sodium bicarbonate solution then brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (2.76g, m.p. 82-84°C). NMR ($CDCl_3$): δ 3.75(2H,s); 4.9(2H,s); 8.3(1H,t); 8.75(1H,bs); 8.9(1H,d). MS: M^+ 248.

Step 2 Preparation of 5-hydroxy-3(5-trifluoromethylpyridin-3-yl) thiazolidin-4-one.

The title compound was prepared by a procedure similar to that described in Example 35, but using 3(5-trifluoromethylpyridin-3-yl)thiazolidin-4-one (2.25g), prepared as described in Step 1 above, in dichloromethane (30ml) and adding sulphuryl chloride (0.73ml) dropwise at 0°C. Immediate precipitation occurred. The mixture was stirred at 5°C for thirty minutes and evaporated under reduced pressure. The residue was hydrolysed directly

using aqueous potassium dihydrogen phosphate solution in tetrahydrofuran by a procedure similar to that described in Example 36, Step 2. The crude product was chromatographed on silica, using dichloromethane-ethanol (19:1) as eluant, to give the title compound (1.16g) as a pale yellow gum. NMR ($CDCl_3$): δ 4.75(1H,d); 5.1(1H,d); 5.75(1H,d); 8.3(1H,d); 8.75(1H,s); 8.95(1H,d). MS: MH^+ 265.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(5-trifluoromethylpyridin-3-yl)-thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, Step 1 but using 5-hydroxy-3(5-trifluoromethylpyridin-3-yl) thiazolidin-4-one (0.50g) from Step 2, t-butyl isocyanate (0.21g), triethylamine (0.21g) and dichloromethane (10ml). Chromatography on silica, using dichloromethane-ethanol (24:1) as eluant, gave the title compound (0.54g, m.p. 161-163°C). NMR ($CDCl_3$): δ 1.35(9H,s); 4.7(1H,d); 4.9(1H,bs); 5.1(1H,dd); 6.2(1H,s); 8.3(1H,m); 8.8(1H,m); 8.95(1H,d). MS: MH^+ 364.

EXAMPLE 42 **Preparation of Compound 143: 5-t-Butylcarbamoyloxy-3(2-trifluoromethylpyridin-4-yl)thiazolidin-4-one**

Step 1 Preparation of ((2-trifluoromethylpyridin-4-yl)aminomethylthio)-acetic acid.

The title compound was prepared by a procedure similar to that described in Example 35, but using 4-amino-2-trifluoromethylpyridine (2.35g), thioglycolic acid (1.33g), 37% aqueous formaldehyde solution (1.18g), p-toluenesulphonic acid (0.025g) and toluene (90ml). After heating for ninety minutes, the mixture was cooled and the precipitate filtered off. This was washed with toluene, then hexane, and dried under reduced pressure to give the title compound as a white solid (3.22g), sufficiently pure for use in Step 2 below. NMR (DMSO-d_6/$CDCl_3$): δ 3.27(2H,s); 4.57(2H,d); 6.82(1H,dd); 7.06(1H,d); 7.68(1H,m); 8.23(1H,d).

The filtrate was evaporated under reduced pressure and the residue chromatographed on silica, using hexane-ethyl acetate (2:1) as eluant, to give the title compound (0.18g, m.p. 63-65°C) of Step 2 below. NMR as below.

Step 2 Preparation of 3(2-trifluoromethylpyridin-4-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 47, Step 2 below, but using ((2-trifluoromethylpyridin-4-yl)amino-methylthio)acetic acid (2.91g), prepared as described in Step 1 above, thionyl chloride (1.30g) triethylamine (2x 1.11g) and dichloromethane (50ml). The reaction mixture was evaporated under reduced pressure, treated with water and extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate solution to remove starting material, then brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (1.67g, m.p. 62-64°C). NMR ($CDCl_3$): δ 3.79 (2H,s); 4.89 (2H,s); 7.75(1H,dd); 7.97(1H,d); 8.71(1H,d). MS: M^+ 248.

Step 3 Preparation of 5-hydroxy-3(2-trifluoromethylpyridin-4-yl)-thiazolidin-4-one.

The title compound was prepared by a procedure similar to that described in Example 40, Step 2, but using 3(2-trifluoromethylpyridine-4-yl)thiazolidin-4-one (1.67g), sulphuryl chloride (0.83g) and dichloromethane (30ml). The reaction was followed by hydrolysis with an aqueous solution of potassium dihydrogen phosphate in tetrahydrofuran. The crude product was chromatographed on silica, using ethyl acetate-hexane (1:1) as eluant, to give the title compound (0.635g) as a yellow oil. NMR ($CDCl_3$): δ 3.58(1H,bs); 4.79(1H,d); 5.09(1H,d); 5.71(1H,s); 7.81(1H,dd); 8.02(1H,d); 8.74(1H,d).

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(2-trifluoromethyl-pyridin-4-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 5-hydroxy-3(2-trifluoromethylpyridin-4-yl) thiazolidin-4-one (0.63g), from Step 3, t-butyl isocyanate (0.47g), triethylamine (0.48g) and dichloromethane (30ml). The reaction mixture was allowed to stand for twenty hours, evaporated under reduced pressure and chromatographed on silica, using ethyl acetate-hexane (1:3) as eluant, to give the title compound (0.35g, m.p. 124-126°C). NMR ($CDCl_3$): δ 1.34(9H,s); 4.75(1H,d); 4.86(1H,bs); 5.11(1H,d); 6.20(1H,s); 7.81(1H,dd); 8.00(1H,d); 8.75(1H,d). MS: MH^+ 364.

EXAMPLE 43 **Preparation of Compound 144: 5-t-Butylcarbamoyloxy-3(4-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(4-trifluoromethylpyridin-2-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 2-amino-4-trifluoromethylpyridine (10.0g), thioglycolic acid (5.70g), 37% aqueous formaldehyde solution (4.80ml) and toluene (100ml). No p-toluenesulphonic acid catalyst was used. The crude product was chromatographed on silica, using ethyl acetate-hexane mixtures as eluant, to give the title compound as a pale yellow oil (2.80g). NMR ($CDCl_3$): δ 3.81(2H,s); 5.13(2H,s); 7.31(1H,d); 8.52(1H,d); 8.65(1H,s).

Step 2 Preparation of 5-hydroxy-3(4-trifluoromethylpyridin-2-yl) thiazolidin-4-one

A stirred solution of 3(4-trifluoromethylpyridin-2-yl)thiazolidin-4-one (2.30g), prepared as described in Step 1 above, in dichloromethane (25ml) was cooled in an ice-bath and treated with sulphuryl chloride (0.75ml) over a period of two minutes. The solution was allowed to warm to room temperature, then treated with saturated sodium bicarbonate solution (50ml). The mixture was stirred for one hour, the organic layer separated, dried over magnesium sulphate and evaporated under reduced pressure to give

the intermediate 5-chloro derivative. This was dissolved in tetrahydrofuran (25ml) and treated with saturated sodium bicarbonate solution (50ml). The mixture was stirred vigorously for four hours, diluted with water and extracted with ether. The extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was recrystallised from chloroform-hexane to give the title compound (2.00g, m.p. 109-110°C, dec). NMR ($CDCl_3$): δ 4.19(1H,bs); 5.09 (1H,d); 5.22(1H,d); 5.78(1H,s); 7.35(1H,d); 8.52(1H,d); 8.67(1H,s).

Step 3 Preparation of
5-t-butylcarbamoyloxy-3(4-trifluoromethylpyridin-2-yl)- thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 5-hydroxy-3(4-trifluoromethylpyridin-2-yl)thiazolidin-4-one (0.80g), from Step 2, t-butyl isocyanate (0.30g), triethylamine (0.42ml), and dichloromethane (5ml). The crude product was triturated with ether-hexane to give the title compound (0.90g). NMR ($CDCl_3$): δ 1.33(9H,s); 4.87(1H,bs); 5.12-5.20(2H,m); 6.29(1H,s); 7.36(1H,d); 8.53(1H,d); 8.71(1H,s). MS: MH^+ 363.

EXAMPLE 44 **Preparation of Compound 145: 5-N(1,1-dimethylprop-2-ynyl)-carbamoyloxy-3(4-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

The title compound was prepared by a procedure similar to that described in Example 35, but using
5-hydroxy-3(4-trifluoromethylpyridin-2-yl)thiazolidin- 4-one (1.10g), prepared as described in Example 43, Steps 1 and 2, triethylamine (0.58ml) and a solution (7.0ml) of 1,1-dimethylprop-2-ynyl isocyanate in toluene, prepared as described in Example 38, Step 1. After three days reaction was incomplete, so a further aliquot (10ml) of the isocyanate solution was added. The reaction was worked up in the usual way. The crude product was chromatographed on silica, using ethyl acetate-hexane mixtures as eluant. Further recrystallisation from carbon tetrachloride-hexane gave the title compound (0.64g, m.p. 119-120°C). NMR ($CDCl_3$): δ 1.54g (6H,s); 2.34(1H,s);

5.10(1H,bs); 5.12-5.21(2H,m); 6.32(1H,s); 7.37(1H,dd); 8.55(1H,d); 8.71(1H,d).

EXAMPLE 45 **Preparation of Compounds 146 and 147: 5-N(1,1-dimethylpropyl) carbamoyloxy-3(4-trifluoromethylpyridin-2-yl) thiazolidin-4-one (Compound 146) and 5-N(1,1-dimethylprop-2-enylcarbamoyloxy-3(4-trifluoromethyl-pyridin-2-yl)thiazolidin-4-one (Compound 147)**

The title compounds were prepared by a procedure similar to that described in Example 39, but initially using 5-N(1,1-dimethylprop-2-ynyl)carbamoyloxy- 3(4-trifluoromethylpyridin-2-yl) thiazolidin-4-one (0.319g), prepared as described in Example 44, and Lindlar's catalyst (0.032g) in ethyl acetate (5ml). After three hours no reaction had occurred, so 10% palladium on carbon catalyst (0.03g) was added. The resultant mixture was hydrogenated for thirty minutes and worked up in the usual manner. The residue was chromatographed on silica, using ethyl acetate-hexane mixtures as eluant, to give firstly title compound 146 (0.049g). NMR ($CDCl_3$): δ 0.87 (3H,t); 1.25(3H,s); 1.27(3H,s); 1.67(2H,m); 4.78(1H,bs); 5.13-5.20(2H,m); 6.29(1H,s); 7.35(1H,dd); 8.56(1H,d); 8.71(1H,d). The second component, title compound 147 (0.219g, m.p. 90-91°C) had NMR ($CDCl_3$): δ 1.41(6H,s); 4.98(1H,bs); 5.03-5.19(4H,m); 5.95(1H,dd); 6.30(1H,s); 7.36(1H,dd); 8.53(1H,d); 8.70(1H,d).

EXAMPLE 46 **Preparation of Compound 148: 3-t-Butylcarbamoyloxy-1(4-methoxypyridin-3-yl)pyrrolidin-2-one**

Step 1 Preparation of 5(4-chlorobutanoylamino)-2-methoxypyridine

A solution of 5-amino-2-methoxypyridine (2.0g) in ether (20ml) was treated, dropwise at 0°C, successively with 4-chlorobutanoyl chloride (2.77g) and triethylamine (1.79g). The mixture was allowed to warm to room temperature, stirred for two hours, poured into water and extracted with ethyl acetate. The extracts were dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (3.70g, m.p. 91-95°C).

Step 2 Preparation of 1(4-methoxypyridin-3-yl)pyrrolidin-2-one

5(4-chlorobutanoylamino-2-methoxypyridine (3.50g), prepared as described in Step 1 above, was added portionwise to a solution of sodium methoxide (from 0.35g sodium) in methanol (30ml), stirred under nitrogen. The reaction mixture was stirred for two hours, diluted with ether and filtered. The filtrate was evaporated under reduced pressure and the residue triturated with ether to give the title compound (2.83g, m.p. 64-65°C). NMR ($CDCl_3$): δ 2.20(2H,p); 2.60(2H,t); 3.84(2H,t); 3.94(3H,s); 6.78(1H,d); 8.10(1H,dd); 8.19(1H,d).

Step 3 Preparation of 3-hydroxy-1(4-methoxypyridin-3-yl)pyrrolidin-2-one

Lithium bis(trimethylsilyl)amide (5.72ml, 1M solution in tetrahydrofuran) was added dropwise to a stirred suspension of 1(4-methoxypyridin-3-yl)-pyrrolidin-2-one (0.5g), prepared as described in Step 2 above, in tetrahydrofuran (20ml), under nitrogen at -78°C. The reaction mixture was stirred for thirty minutes at -78°C, allowed to warm to 0°C, then treated with a stream of oxygen. After one hour, the mixture was poured into saturated aqueous sodium sulphite solution and shaken vigorously for five minutes. It was then extracted with ether and the extracts washed with aqueous sodium sulphite solution then brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using ethyl acetate as eluant, to give crude product, further recrystallised from ethyl acetate to give the title compound (0.155g, m.p. 121-123°C). NMR ($CDCl_3$): δ 2.14(1H,m); 2.64(1H,d); 3.12(1H,bs); 3.76(2H,m); 3.93(3H,s); 4.49(1H,dd); 6.79(1H,d); 8.11(1H,dd); 8.22(1H,d).

Step 4 Preparation of 3-t-butylcarbamoyloxy-1(4-methoxypyridin-3-yl) pyrrolidin-2-one

The title compound was prepared by a procedure similar to that described in Example 35, Step 1, but using 3-hydroxy-1(4-methoxypyridin-3-yl)pyrrolidin-2-one (0.145g), from Step 3, triethylamine (0.39ml), t-butyl isocyanate (0.32ml) and dichloromethane (5ml). After eighteen hours reaction was incomplete, so further aliquots

of triethylamine and isocyanate were added. After a further twenty-four hours the reaction was worked up in the usual way and the crude product chromatographed on silica, using hexane-ethyl acetate (10:3) as eluant, to give the title compound (0.107g, m.p. 110-111°C). NMR ($CDCl_3$): δ 1.34(9H,s); 2.15(1H,m); 2.75(1H,m); 3.80(2H,2d); 3.94(3H,s); 4.90(1H,bs); 5.33(1H,dd); 6.78(1H,d); 8.14(1H,dd); 8.24(1H,d). MS: M^+ 307.

EXAMPLE 47 **Preparation of Compound 149: 5-t-Butylcarbamoyloxy-3(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one**

Step 1 Preparation of ((4,6-dimethylpyrimidin-2-yl)aminomethylthio)acetic acid

The title compound was prepared by a procedure similar to that described in Example 35, but using 2-amino-4,6-dimethylpyrimidine (5.0g), thioglycolic acid (3.74g), 37% aqueous formaldehyde solution (3.29ml), p-toluenesulphonic acid (0.025g) and toluene (70ml). After heating for three hours, the mixture was allowed to cool. The precipitate was filtered off and dried under reduced pressure. Soluble in aqueous sodium bicarbonate solution, it was shown to be the uncyclized title compound (4.0g, m.p. 164-165°C). NMR (DMSO-d_6/$CDCl_3$): δ 2.3(6H,s); 3.35(2H,s); 4.7(2H,d); 6.4(1H,s); 6.85(1H,t).

Step 2 Preparation of 3(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one

A stirred suspension of ((4,6-dimethylpyrimidin-2-yl)aminomethylthio) acetic acid (4.04g), from Step 1 above, in dichloromethane (30ml) was cooled to 5°C, treated with triethylamine (1.90g) them dropwise with thionyl chloride (2.23g). The mixture was stirred at 5°C for two hours, treated with more triethylamine (1.90g), then allowed to warm and stand overnight at room temperature. It was diluted with dichloromethane, washed with water and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica using dichloromethane-ethanol (10:1) as eluant, to give the title compound (2.27g, mp 85-86°C). NMR ($CDCl_3$): δ 2.5(6H,s); 3.8(2H,s); 5.05(2H,s); 6.85(1H,s). MS: MH^+ 210.

Step 3 Preparation of 3(4,6-dimethylpyrimidin-2-yl)-5-hydroxy thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 37 Step 2, but using 3(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (0.5g), from Step 2 above, sulphuryl chloride (0.10ml and 0.09ml) and dichloromethane (10ml). The crude chloro derivative was dissolved in tetrahydrofuran and treated with an aqueous solution of potassium dihydrogen phosphate in a procedure similar to that described in Example 36, Step 2. The crude product was chromatographed on silica, using dichloromethane-ethanol (19:1) as eluant, to give the title compound (0.10g). NMR ($CDCl_3$): δ 2.5(6H,s); 5.1(2H,m); 5.7(1H,s); 6.9(1H,s). MS: MH^+ 226.

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 3(4,6-dimethylpyrimidin-2-yl)-5-hydroxythiazolidin-4-one (0.10g), from Step 3, t-butyl isocyanate (0.048g), triethylamine (0.05g) and dichloromethane (10ml). Chromatography on silica, using dichloromethane-ethanol (49:1) as eluant, gave the title compound (0.10g, m.p. 153-154°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.5(6H,s); 4.9(1H,bs); 5.1(2H,m); 6.2(1H,s); 6.9(1H,s). MS: MH^+ 325.

EXAMPLE 48 **Preparation of Compound 150: 3(5-Bromothiazol-2-yl)-5-t-butylcarbamoyloxy-thiazolidin-4-one**

Step 1 Preparation of 3(5-bromothiazol-2-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 43 Step 1, but using 2-amino-5-bromothiazole (5.0g), thioglycolic acid (2.60g), 37% aqueous formaldehyde solution (2.24ml) and toluene (100ml). The title compound was obtained as a crystalline solid (0.62g). NMR ($CDCl_3$): δ 3.81(2H,s); 5.08(2H,s); 7.42(1H,s).

Step 2 Preparation of 3(5-bromothiazol-2-yl)-5-hydroxythiazolidin-4-one

A stirred solution of 3(5-bromothiazol-2-yl)thiazolidin-4-one (0.62g, prepared as described in Step 1 above) in dichloromethane (10ml) was treated with sulphuryl chloride (0.19ml). The resultant suspension was stirred for one hour, giving a green solution, then evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (25ml), treated with saturated sodium bicarbonate solution (35ml) and the mixture stirred vigorously for five hours. It was then diluted with water and extracted with chloroform (2x50ml). The extracts were washed with water, dried over magnesium sulphate, and evaporated under reduced pressure. The residue was chromatographed on silica, using ethyl acetate-hexane mixtures as eluant, to give the title compound as a pale yellow solid (0.350g).

Step 3 Preparation of 3(5-Bromothiazol-2-yl)-5-t-butylcarbamoyloxy-thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, but using 3(5-bromothiazol-2-yl)-5-hydroxythiazolidin-4-one (0.35g), from Step 2, t-butyl isocyanate (0.123g), triethylamine (0.17ml) and dichloromethane (10ml). The crude product was recrystallised from ethyl acetate-hexane to give the title compound as white needles (0.220g). NMR ($CDCl_3$): δ 1.32(9H,s); 4.83(1H,bs); 5.05-5.13(2H,m); 6.31(1H,s); 7.44(1H,s). MS: M^+(Br=79) 379.

EXAMPLE 49 Preparation of Compound 151: 5-t-Butylcarbamoyloxy-3-(4-chlorobenzothiazol-2-yl)thiazolidin-4-one

Step 1 Preparation of ((4-chlorobenzothiazol-2-yl)aminomethylthio)acetic acid

The title compound was prepared by a procedure similar to that described in Example 47, Step 1, but using 2-amino-4-chlorobenzothiazole (9.20g), thioglycolic acid (4.60g), 37% aqueous formaldehyde solution (3.9ml) and toluene (75ml). No p-toluenesulphonic acid catalyst was used. The

precipitate formed on cooling was filtered off, washed with ethyl acetate and dried to give the title compound as a white solid (8.00g). NMR (DMSO-d_6): δ 3.63 (2H,s); 4.80(2H,s); 7.19(1H,t); 7.46 (1H,d); 7.82(1H,d); 9.10(1H,broad), 12.78(1H,broad).

Step 2 Preparation of 3(4-chlorobenzothiazol-2-yl)thiazolidin-4-one

A stirred suspension of ((4-chlorobenzothiazol-2-yl)aminomethylthio)acetic acid (7.60g),from Step 1, in dichloromethane (70ml) was treated with thionyl chloride (2.1ml). After stirring for thirty minutes, triethylamine (7.6ml) was added and stirring continued for a further one hour. The mixture was diluted with water and extracted with dichloromethane. The extracts were dried over magnesium sulphate, evaporated under reduced pressure and the residue recrystallised from ethyl acetate to give the title compound as a crystalline solid (2.60g, m.p. 229°C). NMR ($CDCl_3$): 3.85(2H,s); 5.28(2H,s); 7.25(1H,t); 7.45(1H,d); 7.71(1H,d).

Step 3 Preparation of 3(4-chlorobenzothiazol-2-yl)-5-hydroxythiazolidin--4-one

The title compound was prepared by a procedure similar to that described in Example 48 Step 2, but using 3(4-chlorobenzothiazol-2-yl)thiazolidin-4-one (3.50g) from Step 2 above, sulphuryl chloride (1.05ml) and dichloromethane (50ml), followed by tetrahydrofuran (50ml) and saturated aqueous sodium bicarbonate solution (50ml). The crude product was recrystallised from toluene to give the title compound (0.45g, m.p. 220°C). NMR ($CDCl_3$): δ 5.27(1H,d); 5.38(1H,d); 5.77(1H,d); 7.11(1H,d); 7.28(1H,t); 7.49(1H,d); 7.76(1H,d).

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(4-chlorobenzothiazol-2-yl) thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35 but using 3(4-chlorobenzothiazol-2-yl)-5-hydroxythiazolidin-4-one (0.300g), from Step 3, t-butyl isocyanate (0.104g), triethylamine (0.14ml) and dichloromethane

(10ml). The crude product was recrystallised from carbon tetrachloride-hexane to give the title compound as a white crystalline solid (0.19g). NMR ($CDCl_3$): δ 1.34(9H,s); 4.83(1H,bs); 5.31(1H,d); 5.39(1H,d); 6.35(1H,d); 7.28(1H,t); 7.49(1H,d); 7.73(1H,d).

EXAMPLE 50 **Preparation of Compound 152: 3-t-Butylcarbamoyloxy-1(2-chlorothien-4-yl)pyrrolidin-2-one**

Step 1 Preparation of 1(2-chlorothien-4-yl)pyrrolidin-2-one

A stirred mixture of 4-bromo-2-chlorothiophene (15.80g), pyrrolidin-2-one (6.80g) and cuprous oxide (11.40g) was heated to 130°C under a nitrogen atmosphere for eight hours. The mixture was cooled and filtered, washing through thoroughly with chloroform. The filtrate was evaporated under reduced pressure and the residue chromatographed on silica, using ethyl acetate-hexane mixtures as eluant, to give the title compound as a white solid. 90% pure, it was used in the next step without further purification. NMR ($CDCl_3$): inter alia, δ 2.10-2.21(2H,m); 2.54(2H,t); 3.76(2H,t); 6.90(1H,d); 7.46(1H,d).

Step 2 Preparation of 1(2-chlorothien-4-yl)-3-hydroxypyrrolidin-2-one

A stirred solution of 1(2-chlorothien-4-yl)pyrrolidin-2-one (1.85g), from Step 1 above, in dry tetrahydrofuran (20ml) was cooled to -74°C under a nitrogen atmosphere and treated dropwise with a solution of lithium bis(trimethylsilyl)amide (11.0ml, 1M solution in toluene). The mixture was stirred for ten minutes, then solid 3-phenyl-N-toluenesulphonyloxaziridine (2.78g), prepared as described in J. Org. Chem., (1988) **53**, 2087, was added in one portion. The mixture was stirred at -74°C for ten minutes, then allowed to warm to room temperature. The reaction was quenched with a mixture of 2M hydrochloric acid (11ml) and brine (50ml), and extracted with ethyl acetate (2x20ml). The extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using ethyl acetate-hexane mixtures, then tetrahydrofuran-hexane mixtures, as eluants. The crude product was triturated with ether to give the title compound as a white crystalline

solid (0.260g). NMR ($CDCl_3$): δ 2.09(1H,m); 2.54(1H,m); 3.63(1H,m), 3.74(1H,m); 4.82(1H,d); 6.95(1H,d); 7.49(1H,m).

Step 3 Preparation of 3-t-butylcarbamoyloxy-1(2-chlorothien-4-yl) pyrrolidin-2-one

A stirred suspension of 1(2-chlorothien-4-yl)-3-hydroxypyrrolidin-2-one (0.26g), from Step 2, in dichloromethane (10ml) was treated with t-butyl isocyanate (0.118g) and triethylamine (0.17ml). After three hours, no reaction had occurred. Tetrahydrofuran (5ml) was added and stirring continued for sixteen hours. Further quantities of isocyanate (0.14ml, 0.4ml and 0.2ml) were added immediately, then after further periods of twenty hours and sixty-eight hours. After a final five hours, the mixture was evaporated under reduced pressure and the residue chromatographed on silica, using ethyl acetate-hexane mixtures as eluant, to give after recrystallisation from ethyl acetate-hexane the title compound (0.12g) as a white crystalline solid. NMR ($CDCl_3$): δ 1.32(9H,s); 2.11(1H,m); 2.71(1H,m); 3.63-3.84(2H,m); 4.78(1H,bs); 5.41(1H,t); 6.99(1H,d); 7.43(1H,d).

EXAMPLE 51 **Preparation of Compound No.153: 5-t-Butylcarbamoyloxy-3 (pyridin-3-yl)thiazolidin-4-one**

Step 1 Preparation of 3(pyridin-3-yl)thiazolidin-4-one

The compound was prepared by a procedure similar to that described in Example 36, Steps 1 and 2, but using 3-aminopyridine (5.0g), thioglycolic acid (4.9g), 37% aqueous formaldehyde solution (4.35ml), p-toluenesulphonic acid (0.025g) and toluene (70ml). The toluene layer was decanted and evaporated under reduced pressure to give the title compound (2.79g) as a pale red solid sufficiently pure for use in Step 2. NMR ($CDCl_3$): δ 3.75(2H,s); 4.85(2H,s); 7.4(1H,m); 8.0(1H,dd); 8.5(1H,dd); 8.7(1H,d).

Step 2 Preparation of 3(pyridin-3-yl)thiazolidin-4-one S-oxide

A solution of 3(pyridin-3-yl)thiazolidin-4-one (2.79g, prepared as described in Step 1 above) in ethanol (30ml) was added to a stirred solution of sodium periodate (3.35g) in water (30ml). The mixture was stirred for four hours, allowed to stand overnight at room temperature and evaporated under reduced pressure. The dry residue was stirred overnight with ethanol and filtered. The extracts were evaporated under reduced pressure to give the title compound (2.75g) as a pale yellow solid sufficiently pure to be used in Step 3. NMR ($DMSO-d_6$): δ 3.6(1H,dd); 4.15(1H,d); 4.85(1H,dd); 5.1(1H,d); 7.45(1H,dd); 7.95(1H,m); 8.4(1H,dd); 8.7(1H,d).

Step 3 Preparation of 5-hydroxy-3(pyridin-3-yl)thiazolidin-4-one

A stirred solution of the sulphoxide (2.75g, prepared as described in Step 2 above) in trifluoroacetic acid (30ml) was treated dropwise with trifluoroacetic anhydride (3.21g), whilst maintaining the temperature below 5°C. The mixture was stirred for a further thirty minutes at 0-5°C, for four hours at 20°C, allowed to stand overnight, then evaporated under reduced pressure. The residue was dissolved in dichloromethane, treated with solid sodium carbonate (portionwise), water (dropwise) and methanol (10ml) until effervescence ceased. The mixture was dried with magnesium sulphate, filtered through 'Hyflo-Supercel' ™ and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (19:1) as eluant, to give the title compound (1.01g, m.p. 150-152°C). NMR ($CDCl_3$): δ 4.7(1H,d); 5.1(1H,dd); 5.6(1H,d); 7.0(1H,d); 7.4(1H,dd); 8.0(1H,m); 8.5(1H,dd); 8.8(1H,d).

Step 4 5-t-Butylcarbamoyloxy-3(pyridin-3-yl)thiazolidin-4-one

By a procedure similar to that described in Example 35, the alcohol (0.50g, prepared as described in Step 3 above) was treated with t-butyl isocyanate, triethylamine and dichloromethane to give, after chromatography, Compound 153 (0.52g, m.p. 59-61°C). NMR ($CDCl_3$): δ 1.3(9H,s); 4.7(1H,d); 5.1(1H,dd); 6.2(1H,d); 7.4(1H,dd); 8.0(1H,m); 8.55(1H,dd); 8.7(1H,d). MS: MH^+ 296.

EXAMPLE 52 **Preparation of Compound 154: 5-t-Butylcarbamoyloxy-3(pyrazin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(pyrazin-2-yl)thiazolidin-4-one

By a procedure similar to that described in Example 51 was obtained, from 2-aminopyrazine (5.0g), the title compound (1.85g, m.p. 115-116°C). NMR ($CDCl_3$): δ 3.8(2H,s); 5.1(2H,s); 8.35(2H,m); 9.7(1H,d). MS: M^+ 181.

Step 2 Preparation of 3(pyrazin-2-yl)thiazolidin-4-one S-oxide

The thiazolidinone (0.5g, prepared as described in Step 1 above) was oxidised by a procedure similar to that described in Example 51 to give the corresponding sulphoxide (0.40g, m.p. 170-171°C). NMR ($CDCl_3$): δ 3.9(2H,m); 5.0(1H,d); 5.3(1H,dd); 8.35(1H,m); 8.45(1H,d); 8.7(1H,d). MS: M^+ 197.

Step 3 Preparation of 5-hydroxy-3(pyrazin-2-yl)thiazolidin-4-one

The sulphoxide (1.11g, prepared as described in Step 2 above) was treated with trifluoroacetic anhydride in trifluoroacetic acid, and the resulting trifluoroacetate hydrolysed, both following procedures similar to those described in Example 51. The product (0.20g, m.p. 125-127°C) was isolated by chromatography on silica, using dichloromethane-ethanol (19:1) as eluant. NMR ($CDCl_3$): δ 5.1(2H,m); 5.75(1H,s); 8.4(2H,m); 8.7(1H,d). MS: MH^+ 198.

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(pyrazin-2-yl)-thiazolidin-4-one

By a procedure similar to that described in Example 51, the alcohol (0.18g, prepared as described in Step 3 above) was converted into Compound 154 (0.15g, m.p. 121-122°C). NMR ($CDCl_3$): δ 1.4(9H,s); 4.85(1H,bs); 5.1(2H,m); 6.3(1H,s); 8.35(1H,t); 8.4(1H,d); 9.7(1H,d). MS: MH^+ 297.

EXAMPLE 53 **Preparation of Compound 155: 5-t-Butylcarbamoyloxy-3(5-trifluoromethylpyridin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(5-trifluoromethylpyridin-2-yl)thiazolidin-4-one

Treatment of 2-amino-5-trifluoromethylpyridine (5.0g) with thioglycolic acid (3.1g), 37% aqueous formaldehyde solution (2.7ml), p-toluenesulphonic acid (0.025g) and toluene (70ml), in a manner similar to that described in Example 51, gave a mixture (7.13g) of the title compound and ((5-trifluoromethylpyridin-2-yl)aminomethylthio)acetic acid in a ratio of 1:2. The mixture was dissolved in dichloromethane (50ml), treated with triethylamine (1.44g), cooled to below 5°C, and the stirred solution treated with thionyl chloride (1.74g) then, after two hours, with triethylamine (1.44g). The mixture was allowed to stand overnight at room temperature, diluted with dichloromethane and washed with water, then brine. The organic phase was dried over magnesium sulphate, evaporated under reduced pressure and chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give the title compound (3.33g, m.p. 77-78°C). NMR ($CDCl_3$): δ 3.8(2H,s); 5.1(2H,s); 7.95(1H,dd); 8.5(1H,d); 8.6(1H,bd). MS: M^+ 248.

Step 2 Preparation of 3(5-trifluoromethylpyridin-2-yl)thiazolidin-4-one S-oxide

The thiazolidinone (3.25g, prepared as described in Step 1 above) was oxidised with sodium periodate by a procedure similar to that described in Example 51 to give the corresponding sulphoxide (3.38g, m.p. 131-133°C). NMR ($CDCl_3$): δ 3.9(2H,m); 5.0(1H,d); 5.4(1H,dd); 8.0(1H,dd); 8.55(1H,d); 8.65(1H,d). MS: MH^+ 265.

Step 3 Preparation of 5-hydroxy-3(5-trifluoromethylpyridin-2-yl)-thiazolidin-4-one

The sulphoxide (2.0g, prepared as described in Step 2 above) was treated with trifluoroacetic anhydride in trifluoroacetic acid and the resultant 5-trifluoroacetate hydrolysed, both according to procedures

similar to those described in Example 51. The product (1.19g, m.p. 130-131°C) was isolated by chromatography on silica, using dichloromethane-ethanol (49:1) as eluant. NMR ($CDCl_3$): δ 5.2(2H,m); 5.75(1H,s); 8.0(1H,dd); 8.55(1H,d); 8.65(1H,bd). MS: MH^+ 265.

Step 4 Preparation of 5-t-butylcarbamoyloxy-3(5-trifluoromethylpyridin--2-yl)thiazolidin-4-one

By a procedure similar to that described in Example 51, the alcohol (0.5g, prepared as described in Step 3 above) was converted into Compound 155 (0.35g, m.p. 189-190°C). NMR ($CDCl_3$): δ 1.3(9H,s); 4.8(1H,bs); 5.2(2H,s); 6.3(1H,s); 8.0(1H,dd); 8.6(1H,d); 8.65(1H,d). MS: MH^+ 364.

EXAMPLE 54 **Preparation of Compound 156: 5-t-Butylcarbamoyloxy-3(4-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one**

Step 1 Preparation of 3(4-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one

2-Amino-4-trifluoromethylpyrimidine (5.0g) was treated with thioglycolic acid, aqueous formaldehyde solution, p-toluenesulphonic acid and toluene in a manner similar to that described in Example 51. The crude product (8.18g) was, however, largely uncyclized ((4-trifluoromethyl-pyrimidin-2-yl)aminomethylthio)acetic acid. NMR ($CDCl_3$): δ 3.4(2H,s); 4.8(2H,s); 8.4(1H,d); 8.6(1H,d). MS: MH^+ 268. This material was cyclized in a manner similar to that described in Example 51 to give the title compound (0.75g, m.p. 117°C), following chromatography on silica using dichloromethane-ethanol (49:1) as eluant. NMR ($CDCl_3$): δ 3.8(2H,s); 5.1(2H,s); 7.45(1H,d); 9.05(1H,d). MS: MH^+ 249.

Step 2 Preparation of 5-hydroxy-3(4-trifluoromethylpyrimidin-2-yl)-thiazolidin-4-one

The thiazolidinone (0.38g, prepared as described in Step 1 above) was chlorinated with sulphuryl chloride, then the total product hydrolysed with potassium dihydrogenphosphate buffer, both using a procedure similar to that described in Example 35, Steps 1-3. The second reaction mixture was

extracted with ethyl acetate, the extracts dried and evaporated under reduced pressure and the residue chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give the title compound (0.21g, m.p. 150-151°C). NMR ($CDCl_3$): δ 5.2(2H,m); 5.7(1H,s); 7.5(1H,d); 9.0(1H,d). MS: MH^+ 266.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(4-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one

By a procedure similar to that described in Example 51, the alcohol (0.20g, prepared as described in Step 2 above) was converted into Compound 156 (0.19g, m.p. 63°C) after chromatography on silica, using dichloromethane-ethanol (97:3) as eluant. NMR ($CDCl_3$): δ 1.3(9H,s); 4.8(1H,bs); 5.1(2H,m); 6.2(1H,s); 7.5(1H,d); 9.0(1H,d). MS: MH^+ 365.

EXAMPLE 55 Preparation of Compound 157: 5-t-Butylcarbamoyloxy-3(6-trifluoromethylpyrimidin-4-yl)thiazolidin-4-one

Step 1 Preparation of 3(6-trifluoromethylpyrimidin-4-yl)thiazolidin-4-one

Following the procedures described in Example 54, 4-amino-6-trifluoromethylpyrimidine (2.16g) was converted into crude ((6-trifluoromethylpyrimidin-4-yl)aminomethylthio)acetic acid (3.89g) and thence into the title compound (1.55g, m.p. 90-91°C) following chromatography on silica, using dichloromethane-ethanol (49:1) as eluant. NMR ($CDCl_3$): δ 3.8(2H,s); 5.1(2H,s); 8.75(1H,s); 9.1(1H,s). MS: M^+ 249.

Step 2 Preparation of 5-hydroxy-3(6-trifluoromethylpyrimidin-4-yl)-thiazolidin-4-one

The thiazolidinone (1.44g, prepared as described in Step 1 above) was converted into the 5-chloro analogue and thence the 5-hydroxy analogue using procedures similar to those described in Example 54. The title compound (1.21g, m.p. 89-91°C) was isolated by chromatography on silica, using dichloromethane-ethanol (49:1) as eluant. NMR ($CDCl_3$): δ 5.1(2H,m); 5.75(1H,s); 8.8(1H,d); 9.15(1H,s). MS: MH^+ 266.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(6-trifluoromethyl-pyridin-4-yl)thiazolidin-4-one

By a procedure similar to that described in Example 51, the alcohol (0.50g, prepared as described in Step 2 above) was converted into Compound 157 (0.19g, m.p. 140-142°C), after chromatography on silica using dichloromethane as eluant. NMR ($CDCl_3$): δ 1.3(9H,s); 4.9(1H,bs); 5.1(2H,m); 6.25(1H,s); 8.8(1H,d); 9.1(1H,s). MS: MH^+ 365.

EXAMPLE 56 **Preparation of Compound 158: 5-t-Butylcarbamoyloxy-3(2,6-bistrifluoromethylpyrimidin-4-yl)thiazolidin-4-one**

Step 1 Preparation of 3(2,6-bistrifluoromethylpyridin-4-yl)-thiazolidin-4-one

By a procedure similar to that described in Example 35, but using 4-amino-2,6-bistrifluoromethylpyridine (0.83g) and appropriate amounts of the other reagents, was obtained the title compound (0.32g), after chromatography on silica, using hexane-ethyl acetate (6:1) as eluant. NMR ($CDCl_3$): δ 3.81(2H,s); 4.93(2H,s); 8.15(2H,s). MS: M^+ 316.

Step 2 Preparation of 5-hydroxy-3(2,6-bistrifluoromethylpyridin-4-yl)-thiazolidin-4-one

By procedures similar to those described in Example 35, Steps 2 and 3 but using the thiazolidinone (0.29g, prepared as described in Step 1 above), was obtained the title compound (0.15g), following chromatography on silica using hexane-ethyl acetate (3:1) as eluant. NMR ($CDCl_3$): δ 4.16(1H,bs); 4.82(2H,d); 5.14(1H,d); 5.73(1H,s); 8.19(2H,s). MS: M^+ 332.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(2,6-bistrifluoromethyl-pyridin-4-yl)thiazolidin-4-one

By a procedure similar to that described in Example 51, the alcohol (0.11g, prepared as described in Step 2 above) was converted into Compound

158 (0.068, m.p. 122-124°C), after chromatography on silica using hexane-ethyl acetate (6:1) as eluant. NMR ($CDCl_3$): δ 1.34(9H,s); 4.79(1H,d); 4.86(1H,bs); 5.16(1H,dd); 6.18 (1H,s); 8.19(2H,s). MS: M^+ 431.

EXAMPLE 57 **Preparation of Compound 159: 5-t-Butylcarbamoyloxy-3(2,2-difluoro-1,3-benzodioxol-5-yl)thiazolidin-4-one**

Step 1 Preparation of 3(2,2-difluoro-1,3-benzodioxol-5-yl)-thiazolidin-4-one

By a procedure similar to that described in Example 35, Step 1, but using 5-amino-2,2-difluoro-1,3-benzodioxole (1.50g), thioglycolic acid (0.80g), 37% aqueous formaldehyde solution (0.70g), p-toluenesulphonic acid (0.025g) and toluene (90ml). After heating for ninety minutes, the mixture was evaporated under reduced pressure, diluted with ether and washed successively with hydrochloric acid (2M), water, aqueous sodium bicarbonate solution, and brine. The organic layer was dried over magnesium sulphate, evaporated under reduced pressure and the residue chromatographed on silica, using hexane-ethyl acetate (4:1) as eluant, to give the title compound (0.52g, m.p. 105-107°C). NMR ($CDCl_3$): δ 3.75(2H,d); 4.79(2H,d); 7.06(2H,m); 7.33(1H,d). MS: M^+ 259.

Step 2 Preparation of 5-hydroxy-3(2,2-difluoro-1,3-benzodioxol-5-yl)-thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, Steps 2 and 3, but using 3(2,2-difluoro-1,3-benzodioxol-5-yl)thiazolidin-4-one (0.49g, prepared as described in Step 1 above), sulphuryl chloride (0.25g) and dichloromethane (20ml). The reaction mixture was evaporated under reduced pressure and the residue hydrolysed with an aqueous solution of potassium dihydrogen phosphate in tetrahydrofuran. The crude product was triturated with hexane to give the title compound (0.44g, m.p. 98-100°C). NMR ($CDCl_3$): δ 4.69(1H,d); 4.95(1H,dd); 5.71(1H,d); 7.10(2H,m); 7.37(1H,d). MS: M^+ 275.

Step 3 Preparation of 5-t-butylcarbamoyloxy-3(2,2-difluoro-1,3-benzodioxol-5-yl)thiazolidin-4-one

The title compound was prepared by a procedure similar to that described in Example 35, Step 4, but using the alcohol (0.10g), prepared as described in Step 2 above, t-butylisocyanate (0.036g), triethylamine (0.037g) and dichloromethane (5ml). Chromatography on silica, using hexane-ethyl acetate (4:1) as eluant, gave Compound 159 (0.064g, m.p. 159-161°C). NMR ($CDCl_3$): δ 1.34(9H,s); 4.62(1H,d); 4.88(1H,bs); 4.96(1H,dd); 6.17(1H,d); 7.10(2H,m); 7.35(1H,d). MS: M^+ 374.

EXAMPLE 58 **Preparation of Compound 160: 5-N(1,1-dimethylprop-2-ynyl) carbamoyloxy-3(2,2-difluoro-1,3-benzodioxol-5-yl)thiazolidin-4-one**

By a procedure similar to that described in Example 57, Step 3, but using 1,1-dimethylprop-2-ynyl isocyanate in place of t-butyl isocyanate, the substrate alcohol (0.30g, prepared as described in Example 57, Step 2) gave Compound 160 (0.21g, m.p. 111-115°C). NMR ($CDCl_3$): δ 1.72(6H,s); 2.37(1H,s); 4.62(1H,d); 4.98(1H,dd); 5.15(1H,bs); 6.21(1H,d); 7.10(2H,m); 7.35(1H,d). MS: M^+ 384.

EXAMPLE 59 **Preparation of Compound 161: 3-t-Butylcarbamoyloxy-1(2,6-dichloropyridin-4-yl)pyrrolidin-2-one**

Step 1 Preparation of 3-hydroxy-1(2,6-dichloropyridin-4-yl)pyrrolidin-2-one

A suspension of 4-amino-2,6-dichloropyridine (4.2g) in 3-hydroxy-tetrahydrofuran-2-one (9.7g) was heated at 180°C for twenty hours and allowed to cool. The residue was dissolved in dichloromethane, washed with water, hydrochloric acid (1M) and brine, dried over magnesium sulphate and evaporated under reduced pressure. This residue was triturated with a little dichloromethane to give the title compound (1.0g), sufficiently pure for use in the next stage. NMR (DMSO-d_6): δ 1.8(1H,m); 2.4(1H,m); 3.6(1H,m); 3.8(1H,m); 4.3(1H,m); 5.9(1H,d); 7.8(2H,s).

Step 2 Preparation of 3-t-butylcarbamoyloxy-1(2,6-dichloropyridin-4-yl)-pyrrolidin-2-one

A solution of the alcohol (0.80g, prepared as described in Step 1 above), triethylamine (0.36g) and t-butylisocyanate (0.36g) in dichloromethane (150ml) was allowed to stand overnight at room temperature. Additional aliquots of triethylamine and t-butylisocyanate were added at one day intervals. After four days in total, the mixture was evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give Compound 161 (0.38g, m.p. 164-166°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.2(1H,m); 2.75(1H,m); 4.3(2H,m); 4.9(1H,bs); 5.35(1H,t); 7.75(2H,s). MS: MH^+ 346, 348, 350.

EXAMPLE 60 **Preparation of Compound 162: 3-t-Butylcarbamoyloxy-1(4-trifluoromethylpyridin-2-yl)pyrrolidin-2-one**

By a procedure similar to that described in Example 59, 2-amino-4-trifluoromethylpyridine (3.24g) was treated with excess 3-hydroxytetrahydrofuran-2-one to give, after chromatography on silica using hexane-ethyl acetate (3:1) as eluant, 3-hydroxy-1(4-trifluoromethylpyridin-2-yl)pyrrolidin-2-one (0.16g). This material was converted into the title compound by a procedure similar to that described in Example 59. Preparative layer chromatography on silica, using chloroform-hexane-methanol (91:5:4) as eluant, and recrystallisation from chloroform-hexane gave Compound 162 (0.024g, m.p. 112-114°C). NMR essentially identical to that given in Example 62, describing an alternative synthesis.

EXAMPLE 61 **Preparation of Compounds 163-165**

By procedures similar to those described in Example 59, the appropriate heterocyclic amines were converted into the hydroxypyrrolidinones and thence into their t-butylcarbamates.

Compound 163

2-Amino-4-trifluoromethylthiazole (1.0g) gave 3-hydroxy-1(4-trifluoromethylthiazol-2-yl)pyrrolidin-2-one (0.35g, m.p. 140-141°C). NMR ($CDCl_3$): δ 2.2(1H,m); 2.7(1H,m); 3.0(1H,bs); 4.0(1H,m); 4.3(1H,m); 4.65(1H,t); 7.5(1H,s). MS: M^+ 252. The t-butylcarbamate, Compound 163, had m.p. 157°C. NMR ($CDCl_3$): δ 1.3(9H,s); 2.2(1H,m); 2.8(1H,m); 4.0(1H,m); 4.3(1H,m); 4.85(1H,bs); 5.5(1H,t); 7.5(1H,s). MS: MH^+ 352.

Compound 164

4-Amino-6-trifluoromethylpyrimidine (5.0g) gave 3-hydroxy-1(6-trifluoromethylpyrimidin-4-yl)pyrrolidin-2-one (0.36g, m.p. 178-180°C). NMR ($CDCl_3$): δ 2.15(1H,m); 2.7(1H,m); 3.05(1H,bs); 3.8(1H,m); 4.3(1H,m); 4.6(1H,m); 8.75(1H,s); 9.1(1H,s). MS: M^+ 247. The t-butylcarbamate, Compound 164 had m.p. 136-137°C. NMR ($CDCl_3$): δ 1.35(9H,s); 2.12(1H,m); 2.7(1H,m); 3.85(1H,m); 4.3(1H,m); 4.9(1H,bs); 5.5(1H,t); 8.8(1H,s); 9.1(1H,s). MS: MH^+ 347.

Compound 165

2-Amino-5-trifluoromethyl-1,3,4-thiadiazole (2.0g) gave 3-hydroxy-1(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)pyrrolidin-2-one (0.42g). NMR ($CDCl_3$): δ 2.3(1H,m); 2.8(1H,m); 4.1(1H,m); 4.4(1H,m); 4.7(1H,t). MS: MH^+ 254. The t-butylcarbamate, Compound 165, had m.p. 184-186°C. NMR ($CDCl_3$): δ 1.35(9H,s); 2.3(1H,m); 2.85(1H,m); 4.15(1H,m); 4.45(1H,m); 4.9(1H,bs); 5.5(1H,t). MS: MH^+ 353.

EXAMPLE 62 **A general route to 3-hydrocarbyl-carbamoyloxypyrrolidinones exemplified with Compound 162: 3-t-Butylcarbamoyloxy-1(4-trifluoromethyl pyridin-2-yl)pyrrolidin-2-one**

Step 1 Preparation of 3-t-butylcarbamoyloxy-tetrahydrofuran-2-one

Boron trifluoride diethyl etherate (1.38g) was added dropwise, over a period of fifteen minutes, to a stirred solution of 3-hydroxytetrahydrofuran-2-one (10.0g) and t-butylisocyanate (9.7g) in dry dichloromethane (300ml), whilst maintaining the temperature below 10°C. The mixture was stirred at room temperature for a further four hours, treated with brine and sufficient aqueous sodium bicarbonate solution to render the aqueous phase basic, then extracted several times with dichloromethane. The extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (18.5g, m.p. 104-106°C). NMR ($CDCl_3$): δ 1.34(9H,s); 2.28(1H,m); 2.73(1H,m); 4.28(1H,dt); 4.46(1H,dt); 4.90(1H,bs); 5.31(1H,t). MS: M^+ 201.

The addition can also be catalysed using triethylamine or gaseous hydrogen chloride in place of boron trifluoride. However a rearrangement product can be formed in variable amounts which can necessitate purification of the desired material, for example by chromatography on silica using hexane-ethyl acetate (3:1) as eluant.

Step 2 Preparation of 2-t-butylcarbamoyloxy-4-iodo-N(4-trifluoromethyl-pyridin-2-yl)butanamide.

A stirred solution of 3-t-butylcarbamoyloxy-tetrahydrofuran-2-one (1.0g, prepared as described in Step 1 above) in dry dichloromethane (25ml) was placed under nitrogen and kept dark with an aluminium foil shroud. It was treated dropwise with iodotrimethylsilane (1.0g), allowed to stand overnight at room temperature, treated with chlorotrimethylsilane (1.09g) and stirred for a further three hours. It was then cooled to 0°C and treated dropwise with oxalyl chloride (0.63g) and N,N-dimethylformamide (0.05g). After stirring for thirty minutes at 0°C and a further two hours at 20°C, the mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (25ml) and treated successively, with stirring, with pyridine (2.36g), 4-dimethylaminopyridine (0.06g) and

2-amino-4-trifluoromethylpyridine (0.89g). The mixture was allowed to stand overnight at room temperature, diluted with dichloromethane, washed with hydrochloric acid (2M) and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (99:1) as eluant, to give the title compound (1.11g, m.p. 83-85°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.5(2H,m); 3.25(2H,t); 5.0(1H,bs); 5.3(1H,dd); 7.3(1H,dd); 7.45(1H,d); 8.55(1H,bs); 8.8 (1H,bs). MS: M^+ 473.

Step 3 Preparation of 3-t-butylcarbamoyloxy-1(4-trifluoromethyl-pyridin-2-yl)pyrrolidin-2-one

Sodium hydride (0.090g, 55% suspension in mineral oil) was added portionwise to a stirred solution of 2-t-butylcarbamoyloxy-4-iodo-N-(4-trifluoromethylpyridin-2-yl)butanamide (0.97g, prepared as described in Step 2 above) in dry tetrahydrofuran (10ml). After stirring for a further fifteen minutes, the mixture was poured on to water and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (49:1) as eluant, to give Compound 162 (0.45g, m.p. 115.5-116.5°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.15(1H,m); 2.7(1H,m); 3.9(1H,m); 4.25(1H,m); 4.9(1H,bs); 5.45(1H,t); 7.3(1H,dd); 8.55(1H,d); 8.75(1H,s). MS: MH^+ 346.

EXAMPLE 63 **Preparation of Compounds 166-171**

By procedures similar to those described in Example 62, the appropriate heterocyclic amines were converted into the pyrrolidinone carbamates via the open-chain iodo-amides.

Compound 166

4-Amino-2-trifluoromethylpyridine (1.20g), scaled to 3-t-butyl-carbamoyloxy-tetrahydrofuran-2-one (1.50g) and corresponding quantities of other reagents/solvents, gave 2-t-butylcarbamoyloxy-4-iodo-N(2-trifluoro-methylpyridin-4-yl)butanamide (1.15g, contaminated with starting lactone).

NMR ($CDCl_3$) for product only: δ 1.39(9H,s); 2.41(2H,m); 3.26(2H,m); 5.03(1H,bs); 5.21(1H,m); 7.67(1H,dd); 7.83(1H,d); 8.58(1H,d); 8.93(1H,bs). Cyclisation of this crude material with sodium hydride in tetrahydrofuran gave Compound 166 (0.20g, m.p. 101-104°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.20(1H,m); 2.77(1H,m); 3.82(1H,m); 3.93(1H,dt); 4.90(1H,s); 5.40(1H,t); 7.86(1H,dd); 8.03(1H,d); 8.69(1H,d). MS: M^+ 345.

Compound 167

4-Amino-2-chloropyridine (0.32g), scaled to 3-t-butylcarbamoyloxy-tetrahydrofuran-2-one (0.50g) etc., gave 2-t-butylcarbamoyloxy-4-iodo-N(2-chloropyridin-4-yl)butanamide (0.65g, m.p. 65-67°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.4(2H,m); 3.25(2H,m); 5.05(1H,bs); 5.2(1H,t); 7.3(1H,dd); 7.55(1H,d); 8.2(1H,d); 8.9(1H,bs). MS: MH^+ 440, 442. Base catalysed cyclisation of this material (0.58g) gave Compound 167 (0.18g, m.p. 152-154°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.15(1H,m); 2.75(1H,m); 3.75(2H,m); 4.9(1H,bs); 5.4(1H,t); 7.65(2H,m); 8.35(1H,m). MS: MH^+ 312,314.

Compound 168

2-Amino-4-chloropyridine (0.40g), scaled to lactonecarbamate (0.63g) etc., gave 2-t-butylcarbamoyloxy-4-iodo-N(4-chloropyridin-2-yl)butanamide (0.215g, m.p. 39-42°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.47(2H,m); 3.22(2H,t); 4.98(1H,bs); 5.24(1H,dd); 7.10(1H,dd); 8.18(1H,d); 8.32(1H,d); 8.62(1H,bs). MS: M^+ 439, 441. Base-catalysed cyclisation of this material (0.17g) gave Compound 168 (0.055g, m.p. 133-135°C). NMR ($CDCl_3$): δ 1.37 (9H,s); 2.09(1H,m); 2.68(1H,m); 3.85(1H,m); 4.23(1H,dt); 4.90(1H,bs) 5.42(1H,t); 7.09(1H,dd); 8.26(1H,d); 8.52(1H,d). MS: M^+ 311, 313.

Compound 169

4-Amino-2-iodopyridine (0.90g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.26g, m.p. 76-77°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.35(2H,m); 3.25(2H,m); 5.15(1H,t); 5.2(1H,bs); 7.4(1H,dd); 7.8(1H,d); 8.15(1H,d); 9.15(1H,bs). MS: MH^+ 532. Base-

catalysed cyclisation of this material (0.22g) gave Compound 169 (0.14g, m.p. 69-70°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.15(1H,m); 2.7(1H,m); 3.8(2H,m); 5.0(1H,bs); 5.35(1H,t); 7.7(1H,dd); 8.0(1H,d); 8.3(1H,d). MS: MH^+ 404.

Compound 170

2-Amino-4,6-bistrifluoromethylpyridine (1.72g), scaled to lactonecarbamate (1.50g) etc, gave the corresponding iodo-amide (0.94g, m.p. 127-131°C). NMR ($CDCl_3$): δ 1.39(9H,s); 2.46(2H,m); 3.24(2H,t); 5.03(1H,bs); 5.26(1H,dd); 7.64(1H,d); 8.74(1H,d); 8.86(1H,bs). MS: M^+ 541. Base-catalysed cyclisation of this material (0.15g) gave Compound 170 (0.098g, m.p. 123-126°C). NMR ($CDCl_3$): δ 1.37(9H,s); 2.15(1H,m); 2.72(1H,m); 3.92(1H,m); 4.33(1H,dt); 4.90(1H,bs); 5.48(1H,t); 7.63(1H,s); 8.99(1H,s). MS: MH^+ 414.

Compound 171

2-Amino-6-chloro-4-trifluoromethylpyridine (1.08g), scaled to lactonecarbamate (1.0g) etc.,gave the corresponding iodo-amide (1.14g, m.p. 115-116°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.5(2H,m); 3.2(2H,t); 5.0(1H,bs); 5.25(1H,dd); 7.35(1H,s); 8.45(1H,s); 8.7(1H,bs). MS: MH^+ 508, 510. Base-catalysed cyclisation of this material (0.50g) gave Compound 171 (0.21g, m.p. 149-151°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.1(1H,m); 2.7(1H,m); 3.85(1H,m); 4.25(1H,m); 4.9(1H,bs); 5.45(1H,t); 7.3(1H,s); 8.7(1H,s). MS: MH^+ 379, 381.

EXAMPLE 64 **Preparation of Compound 172: 3-t-Butylcarbamoyloxy-1(pyridin-3-yl)pyrrolidin-2-one**

By a procedure similar to that described in Example 62, 3-aminopyridine (0.47g), scaled to 3-t-butylcarbamoyloxytetrahydrofuran-2-one (1.0g) etc., gave a crude product (3.1g) containing approximately 20 mole % of 2-t-butylcarbamoyloxy-4-iodo-N(pyridin-3-yl)-butanamide. The desired product was apparently unstable in the mixture and to chromatography on silica. NMR ($CDCl_3$) for product only: δ 1.38(9H,s);

2.46(2H,m); 3.25(2H,t); 5.12(1H,bs); 5.25(1H,dd); 7.29(1H,m): 8.17(1H,dd); 8.36(1H,dd); 8.58(1H,d). Base-catalysed cyclisation of this crude material gave Compound 172 (0.18g, m.p. 129-131°C) after several chromatographic separations on silica using dichloromethane-ethanol (19:1) as eluant. NMR ($CDCl_3$): δ 1.35(9H,s); 2.12(1H,m); 2.77(1H,m); 3.86(2H,m); 4.90(1H,bs); 5.36(1H,t); 7.33(1H,dd); 8.28(1H,m); 8.44(1H,dd); 8.76(1H,d). MS: M^+ 277.

EXAMPLE 65 **Preparation of Compound 173: 3-t-Butylcarbamoyloxy-1(pyridin-3-yl)pyrrolidin-2-one N-oxide**

A stirred solution of the pyridine (0.090g, prepared as described in Example 64) in dichloromethane (10ml) was treated with m-chloroperbenzoic acid (0.12g, 55%). After being allowed to stand overnight at room temperature, the mixture was diluted with dichloromethane, washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (19:1) as eluant, to give Compound 173 (0.070g, m.p. 224-225°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.17(1H,m); 2.75(1H,m); 3.72(2H,m); 4.92(1H,bs); 5.34(1H,t); 7.27(1H,dd); 7.85(1H,d); 8.05(1H,dd); 8.63(1H,t). MS: M^+ 293.

EXAMPLE 66 **Preparation of Compounds 174-182 and Compound 164 (alternative method)**

By procedures similar to those described in Example 62, the appropriate heterocyclic amines were converted into the pyrrolidinone carbamates via the open-chain iodo-amides.

Compound 174 2-Amino-4-trifluoromethylpyrimidine (0.41g), scaled to lactonecarbamate (0.50g) etc., gave the corresponding iodo-amide, (0.16g, contaminated with starting lactonecarbamate). NMR ($CDCl_3$) for product only: δ 1.3(9H,s); 2.3(2H,m); 3.3(2H,t); 4.9(1H,bs); 5.3(1H,t); 7.4(1H,d); 8.95(1H,d); 8.8(1H,bs). Base-catalysed cyclisation of this material gave Compound 174 (0.018g, m.p. 100-101°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.1(1H,m); 2.7(1H,m); 3.9(1H,m); 4.3(1H,m); 4.9(1H,bs); 5.4(1H,t); 7.4(1H,d); 9.0(1H,d). MS: MH^+ 347.

Compound 175

5-Aminopyrimidine (0.52g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.38g, m.p. 77-79°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.4(2H,m); 3.25(2H,m); 5.05(1H,bs); 5.25(1H,dd); 8.65(1H,bs); 9.0(3H,s). MS: MH^+ 407. Base catalysed cyclisation of this material (0.34g) gave Compound 175 (0.17g, m.p. 171-173°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.2(1H,m); 2.8(1H,m); 3.85(2H,m); 5.0(1H,bs); 5.4(1H,t); 9.05(1H,s); 9.15(2H,s). MS: MH^+ 279.

Compound 176

2-Aminopyrazine (0.71g), scaled to lactonecarbamate (1.50g) etc., gave the corresponding iodo-amide (0.32g, m.p. 113-115°C). NMR ($CDCl_3$): δ 1.38(9H,s); 2.47(2H,m); 3.33(2H,t); 4.97(1H,bs); 5.28(1H,dd); 8.27(1H,dd); 8.39(1H,d); 8.56(1H,bs); 9.56(1H,d). MS: M^+ 406. Base-catalysed cyclisation of this material (0.26g) gave Compound 176 (0.11g, m.p. 146-149°C). NMR ($CDCl_3$): δ 1.36(9H,s); 2.14(1H,m); 2.74(1H,m); 3.84(1H,m); 4.18(1H,dt); 4.92(1H,s); 5.45(1H,t); 8.35(2H,m); 9.76(1H,d). MS: M^+ 278.

Compound 177

4-Amino-6-chloropyrimidine (0.71g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.65g, m.p. 175-176°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.45(2H,m); 3.2(2H,t); 5.0(1H,bs); 5.25(1H,dd); 8.25(1H,s); 8.65(1H,s); 8.8(1H,bs). MS: MH^+ 441, 443. Base-catalysed cyclisation of this material (0.54g) gave Compound 177 (0.16g, m.p. 117°C). NMR ($CDCl_3$): δ 1.35(1.35(9H,s); 2.15(1H,m); 2.7(1H,m); 3.8(1H,m); 4.25(1H,m); 4.9(1H,s); 5.4(1H,t); 8.5(1H,d); 8.75(1H,s). MS: M^+ 312, 314.

Compound 178

4-Amino-6-chloro-2-methylthiopyrimidine (1.02g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (1.08g, m.p. 131-132°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.3(2H,m); 2.55(3H,s);

3.2(2H,t); 5.0(1H,bs); 5.2(1H,dd); 7.9(1H,s); 8.7(1H,bs). MS: MH^+ 486, 488. Base-catalysed cyclisation of this material (0.88g) gave Compound 178 (0.065g, m.p. 165-167°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.1(1H,m); 2.55(3H,s); 2.65(1H,m); 3.8(1H,m); 4.25(1H,m); 4.9(1H,bs); 5.4(1H,t); 8.1(1H,s). MS: MH^+ 359, 361.

Compound 164 (Alternative method)

4-Amino-6-trifluoromethylpyrimidine (1.06g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.76g, m.p. 169-171°C). NMR (DMSO-d_6): δ 1.3(9H,s); 2.4(2H,m); 3.3(2H,t); 5.15(1H,dd); 6.1(1H,bs); 8.55(1H,s); 9.0(1H,s); 10.9(1H,bs). MS: MH^+ 475. Base-catalysed cyclisation of this material (0.60g) gave Compound 164 (0.21g, m.p. 137°C). NMR and MS were identical to values given for this compound, prepared as described in Example 61.

Compound 179

4-Amino-6(2,2-difluoroethoxy)pyrimidine (0.86g, m.p. 127°C) was made by treating 4-amino-6-chloropyrimidine (2.50g) with sodium 2,2-difluoroethoxide in tetrahydrofuran. Reaction of it (0.91g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (1.28g, m.p. 42-44°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.5(2H,m); 3.2(2H,t); 4.6(2H,dt); 5.0(1H,bs); 5.2(1H,dd); 6.1(1H,tt); 7.65(1H,s); 8.5(1H,s); 8.7(1H,bs). MS: MH^+ 487. Base-catalysed cyclisation of this material (1.09g) gave Compound 179 (0.43g, m.p. 49-51°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.1(1H,m); 2.7(1H,m); 3.8(1H,m); 4.25(1H,m); 4.6(2H,dt); 4.9(1H,bs); 5.4(1H,t); 6.1(1H,tt); 7.9(1H,s); 8.6(1H,s). MS: MH^+ 359.

Compound 180

4-Amino-6(2,2,2-trifluoroethoxy)pyrimidine (0.61g, m.p. 113°C) was made by treating 4-amino-6-chloropyrimidine (1.0g) with sodium 2,2,2-trifluoroethoxide in N,N-dimethylformamide. Reaction of it (0.59g), scaled to lactonecarbamate (0.58g) etc., gave the corresponding iodo-amide (0.55g, m.p. 46-47°C). NMR ($CDCl_3$): δ 1.4(9H,s); 2.5(2H,m); 3.2(2H,t);

4.8(2H,m); 4.95(1H,bs); 5.25(1H,dd); 7.7(1H,s); 8.5(1H,s); 8.65(1H,bs). MS: MH^+ 504. Base-catalysed cyclisation of this material (0.44g) gave Compound 180 (0.21, m.p. 100-101°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.1(1H,m); 2.7(1H,m); 3.8(1H,m); 4.25(1H,m); 4.8(2H,q); 4.9(1H,bs); 5.4(1H,t); 7.9(1H,s); 8.6(1H,s). MS: MH^+ 377.

Compound 181

4-Amino-6-difluoromethoxypyrimidine (0.17g, m.p. 152-154°C) was made by passing chlorodifluoromethane into a solution of 4-amino-6-hydroxypyrimidine (0.5g) in aqueous dioxan at 70°C, in the presence of sodium hydroxide. Reaction of it (0.94g), scaled to lactonecarbamate (1.06g) etc., gave the corresponding iodo-amide (1.01g, pale yellow gum). NMR ($CDCl_3$): δ 1.4(9H,s); 2.5(2H,m); 3.2(2H,t); 5.0(1H,bs); 5.25(1H,dd); 7.48(1H,t); 7.75(1H,s); 8.5(1H,s); 8.75(1H,bs). MS: MH^+ 473. Base-catalysed cyclisation of this material (0.80g) gave Compound 181 (0.23g, m.p. 140-141°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.1(1H,m); 2.7(1H,m); 3.8(1H,m); 4.3(1H,m); 4.9(1H,bs); 5.4(1H,t); 7.5(1H,t); 8.0(1H,s); 9.6(1H,s). MS: MH^+ 345.

Compound 182

4-Amino-6-difluoromethoxy-2-methoxypyrimidine (1.73g, m.p. 112-113°C) was made by passing chlorodifluoromethane into a solution of 4-amino-6-hydroxy-2-methoxypyrimidine (4.0g) in aqueous dioxan at 70°C, in the presence of sodium hydroxide. Reaction of it (0.84g), scaled to lactonecarbamate (0.80g) etc., gave the corresponding iodo-amide (0.33g, m.p. 54-55°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.4(2H,m); 3.2(2H,t); 3.95(3H,s); 4.95(1H,bs); 5.2(1H,dd); 7.4(1H,s); 7.45(1H,t); 8.6(1H,s). MS: M^+ 502. Base-catalysed cyclisation of this material (0.29g) gave Compound 182 (0.12g, m.p. 107-108°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.1(1H,m); 2.7(1H,m); 3.8(1H,m); 4.0(3H,s); 4.25(1H,m); 4.95(1H,bs); 5.4(1H,t); 7.45(1H,t); 7.6(1H,s). MS: MH^+ 375.

EXAMPLE 67 **Preparation of Compounds 183-189**

By procedures similar to those described in Example 62, the appropriate heterocyclic amines were converted into the pyrrolidinone carbamates via the open-chain iodo-amides.

Compound 183

2-Amino-5-bromothiazole (0.45g), scaled to lactonecarbamate (0.50g) etc., gave the corresponding iodo-amide (0.45g, m.p. 59-61°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.5(2H,m); 3.2(2H,t); 4.9(1H,bs); 5.3(1H,dd); 7.4(1H,s); 10.0(1H,vbs). MS: MH^+ 490, 492. Base-catalysed cyclisation of this material (0.40g) gave Compound 183 (0.14g, m.p. 193-194°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.2(1H,m); 2.8(1H,m); 3.9(1H,m); 4.2(1H,m); 4.9(1H,bs); 5.5(1H,t); 7.4(1H,s). MS: M^+ 361, 363.

Compound 184

2-Amino-5-trifluoromethylthiazole (5.57g of hydrochloride salt after appropriate work-up) was made by treating 2-aminothiazole 5-carboxylic acid (8.20g) with sulphur tetrafluoride and hydrogen fluoride at 120°C. The anhydrous free base (0.42g), liberated from the hydrochloride salt with aqueous sodium bicarbonate solution, scaled to lactonecarbamate (0.50g) etc, gave the corresponding iodo-amide (0.52g, m.p. 50-52°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.5(2H,m); 3.25(2H,t); 4.95(1H,bs); 5.3(1H,dd); 7.85(1H,s); 10.6(1H,bs). MS: MH^+ 480. Base-catalysed cyclisation of this material (0.45g) gave Compound 184 (0.13g, m.p. 189-190°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.25(1H,m); 2.8(1H,m); 4.0(1H,m); 4.3(1H,m); 4.9(1H,bs); 5.5(1H,t); 7.8(1H,m). MS: MH^+ 352.

Compound 185

2-Amino-5-iodothiazole (1.30g, as hydrochloride salt), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.29g, m.p. 50-60°C, decomp). NMR ($CDCl_3$): δ 1.32(9H,s); 2.45(2H,m); 3.22(2H,t); 4.85(1H,bs); 5.30(1H,dd); 7.56(1H,s). MS: MH^+ 538. Base-catalysed

cyclisation of this material (0.22g) gave Compound 185 (0.14g, m.p. 199-201°C). NMR ($CDCl_3$): δ 1.34(9H,s); 2.20(1H,m); 2.77(1H,m); 3.93(1H,m); 4.24(1H,dt); 4.87(1H,bs); 5.48(1H,t); 7.53(1H,s). MS: M^+ 409.

Compound 186

2-Amino-5-chlorothiazole (0.85g, as hydrochloride salt), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.50g, m.p. 119-122°C). NMR ($CDCl_3$): δ 1.34(9H,s); 2.46(2H,m); 3.22(2H,t); 4.90(1H,bs); 5.32(1H,dd); 7.34(1H,s). Base-catalysed cyclisation of this material (0.39g) gave Compound 186 (0.19g, m.p. 191-192°C). NMR ($CDCl_3$): δ 1.35(9H,s); 2.20(1H,m); 2.77(1H,m); 3.92(1H,m); 4.24(1H,dt); 4.87(1H,bs); 5.48(1H,t); 7.32(1H,s). MS: M^+ 317, 319.

Compound 187

5-Amino-3-trifluoromethylisoxazole (0.76g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.91g, m.p. 100-102°C). NMR ($CDCl_3$): δ 1.35 (9H,s); 2.4(2H,m); 3.25(2H,m); 5.05(1H,bs); 5.3(1H,dd); 6.65(1H,s). MS: MH^+ 464. Base-catalysed cyclisation of this material (0.79g) gave Compound 187 (0.19g, m.p. 181-182°C). NMR ($CDCl_3$): δ 1.3(9H,s); 2.2(1H,m); 2.8(1H,m); 3.9(1H,m); 4.15(1H,m); 4.9(1H,bs); 5.4(1H,t); 6.8(1H,s). MS: M+ 335.

Compound 188

2-Amino-4-trifluoromethyloxazole (0.80g), scaled to lactonecarbamate (2.0g) etc., gave the corresponding iodo-amide (0.30g, brown oil). NMR($CDCl_3$): δ 1.32(9H,s); 2.40(2H,m); 3.22(2H,m); 5.0(1H,s); 5.27(1H,t); 7.79(1H,s); 9.30(1H,s). MS: M^+ 463. Base-catalysed cyclisation of this material (0.20g) gave Compound 188 (0 .095g, m.p. 150-151°C). NMR ($CDCl_3$): δ 1.32 (9H,s); 2.21(1H,m); 2.72(1H,m); 3.90(1H,m); 4.13(1H,m); 4.88(1H,bs); 5.35(1H,t); 7.83(1H,s).

Compound 189

5-Amino-2,2-difluoro-1,3-benzodioxole (0.79g), scaled to lactonecarbamate (1.0g) etc., gave the corresponding iodo-amide (0.53g, m.p. 135-135°C). NMR ($CDCl_3$): δ 1.37(9H,s); 2.43(2H,m); 3.25(2H,t); 4.94(1H,bs); 5.20(1H,dd); 6.99(2H,m); 7.58(1H,dd); 8.32(1H,bs). MS: M^+ 484. Base-catalysed cyclisation of this material (0.47g) gave Compound 189 (0.20g m.p. 147-148°C). NMR ($CDCl_3$): δ 1.34(9H,s); 2.08(1H,m); 2.74(1H,m); 3.80(2H,m); 4.90(1H,bs); 5.35(1H,t); 7.05(1H,d); 7.14(1H,dd); 7.71(1H,d), MS: M^+ 356.

EXAMPLE 68 **A general route to 3(N(hydrocarbamoyl)alkylamino)- and 3(N(alkanoyl)alkylamino)-pyrrolidinones exemplified by Compounds 190 and 191**

Compound 190: 3(N(t-butylcarbamoyl)methylamino-1(4-trifluoromethyl-pyridin-2-yl)pyrrolidin-2-one

Step 1 Preparation of 2,4-dibromo-N(4-trifluoromethylpyridin-2-yl)-butanamide.

A solution of 2-amino-4-trifluoromethylpyridine (5.00g) and triethylamine (3.43g) in dry tetrahydrofuran (50ml) was added dropwise, over ten minutes, to a stirred solution of 2,4-dibromobutanoyl chloride (9.51g) in dry tetrahydrofuran (50ml), whilst maintaining the temperature below 5°C. The mixture was allowed to stir overnight at room temperature, diluted with hydrochloric acid (1M) and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using hexane-ethyl acetate (5:1) as eluant, to give the title compound (10.09g, yellow gum) sufficiently pure for use in Step 2 below. Rechromatographed material had NMR ($CDCl_3$): δ 2.57(1H,m); 2.74(1H,m); 3.62(2H,m); 4.71(1H,dd); 7.33(1H,dd); 8.49(3H,d+s); 8.84(1H,bs). MS: M^+ 388.

Step 2 Preparation of 3-bromo-1(4-trifluoromethylpyridin-2-yl)pyrrolidin--2-one

Sodium hydride (0.82g, 55-65% dispersion in mineral oil) was added portionwise to a stirred solution of the substrate (7.28g, prepared as described in Step 1 above) in dry tetrahydrofuran (150ml). The mixture was stirred for one hour, diluted carefully with water and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulphate, and evaporated under reduced pressure. The residue was chromatographed on silica, using hexane-ethyl acetate (7:1) as eluant, to give the title compound (3.90g, m.p. 43-47°C). NMR ($CDCl_3$): δ 2.48(1H,m); 2.74(1H,m); 4.21(2H,m); 4.66(1H,dd); 7.32(1H,dd); 8.56(1H,d); 8.74(1H,s). MS: M^+ 308,310.

Step 3 Preparation of 3-methylamino-1(4-trifluoromethyl-pyridin-2-yl)pyrrolidinone

Gaseous methylamine was bubbled through a stirred solution of the substrate (2.15g, prepared as described in Step 2 above) in dry tetrahydrofuran (100ml) for one hour. The mixture was diluted with water, and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulphate, and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (19:1) as eluant, to give the title compound (1.30g, m.p. 79-81°C). NMR ($CDCl_3$): δ 1.96(1H,m); 2.50(1H,m); 2.56(3H,s); 3.61(1H,dd); 3.86(1H,m); 4.24(1H,m); 7.26(1H,dd); 8.51(1H,d); 8.74(1H,d). MS: M^+ 259.

Step 4 Preparation of 3(N(t-butylcarbamoyl)methylamino)-1(4-trifluoro-methylpyridin-2-yl)pyrrolidin-2-one

A stirred solution of substrate (0.30g, prepared as described in Step 3 above) in dichloromethane (20ml) was treated successively with triethylamine (0.12g) and t-butylisocyanate (0.115g). The residue was allowed to stir for one hour, diluted with dichloromethane and washed with water and brine. The extracts were dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on

silica, using hexane-ethyl acetate (1:1) as eluant, to give Compound 190 (0.28g, m.p. 152-155°C). NMR ($CDCl_3$): δ 1.38(9H,s); 2.13(1H,m); 2.45(1H,m); 2.85(3H,s); 3.81(1H,m); 4.30(1H,m); 4.44(1H,bs); 5.29(1H,dd); 7.26(1H,dd); 8.53(1H,d); 8.78(1H,s). MS: M^+ 358

Compound 191:
3((N(3,3-dimethylbutanoyl))methylamino)-1(4-trifluoromethylpyridin-2-yl)-pyrrolidin-2-one

A stirred solution of 3-methylamino-1(4-trifluoromethylpyridin-2-yl)-pyrrolidin-2-one (0.30g, prepared as described in Example 68, Step 3, above) in dichloromethane (20ml) was treated successively with triethylamine (0.13g) and 3,3-dimethylbutanoyl chloride (0.16g). After one hour, the mixture was diluted with dichloromethane, washed with water and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using hexane-ethyl acetate (1:1) as eluant, to give Compound 191 (0.31g, m.p. 47-53°C). NMR ($CDCl_3$): δ 1.31(9H,s); 2.31(4H,m+s); 3.09(3H,s); 3.88(1H,m); 4.32(1H,m); 5.22(1H,t); 7.26(1H,dd); 8.52(1H,d); 8.78(1H,s). MS: M+ 357.

EXAMPLE 69 **Preparation of Compounds 192 and 193**

The title compounds were prepared by procedures similar to those described in Example 68 but using 2-amino-5-trifluoromethylthiazole (prepared as described in Example 67) in Step 1. This amine (2.17g) gave 2,4-dibromo-N(5-trifluoromethylthiazol-2-yl)butanamide (4.50g, m.p. 113-115°C). NMR ($CDCl_3$): δ 2.55(2H,m); 3.65(2H,t); 4.8(1H,dd); 8.0(1H,d). MS: MH^+ 395, 397, 399. Base-catalysed cyclisation of this material (4.27g) gave 3-bromo-1(5-trifluoromethylthiazol-2-yl)pyrrolidin-2-one (2.68g, m.p. 105-106°C). NMR ($CDCl_3$): δ 2.6(1H,m); 2.85(1H,m); 4.25(2H,m); 4.7(1H,dd); 7.8(1H,s). MS: M^+ 314, 316. This material (1.0g) was treated with methylamine in tetrahydrofuran to give 3-methylamino-1(5-trifluoro-methylthiazol-2-yl)pyrrolidin-2-one (0.24g, m.p. 108-109°C). NMR ($CDCl_3$): δ 2.1(1H,m); 2.6(4H,m); 3.7(1H,t); 4.0(1H,m); 4.3(1H,m); 7.8(1H,s). MS: M^+ 265.

Samples of this amine (0.12g) were treated with t-butyl isocyanate to give Compound 192 (0.07g, m.p. 186-187°C) and with 3,3-dimethylbutanoyl chloride to give Compound 193 (0.15g, m.p. 123°C). Compound 192 had NMR ($CDCl_3$): δ 1.35(9H,s); 2.3(1H,m); 2.6(1H,m); 2.9(3H,s); 3.9(1H,m); 4.35(1H,m); 4.45(1H,bs); 5.1(1H,dd); 7.8(1H,d). MS: M^+ 364. Compound 193 had NMR ($CDCl_3$): δ 1.1(9H,s); 2.35(1H,m); 2.6(1H,m); 3.15(3H,s); 4.0(1H,m); 4.35(1H,m); 4.85(1H,bs); 7.8(1H,d). MS: MH^+ 364.

EXAMPLE 70 **Preparation of Compounds 194 and 195**

The title compounds were prepared by procedures similar to these described in Example 68 but using 5-amino-2,2-difluoro-1,3-benzodioxole in Step 1. In this case the intermediate bromopyrrolidine (and chloro contaminant) was converted into the corresponding iodide, by treatment with sodium iodide in acetone, before introduction of the alkylamine functionality. In some cases, higher yields can be obtained.

The aminobenzodioxole (2.00g) gave the dibromobutanamide (2.46g). NMR ($CDCl_3$): δ 2.56(1H,m); 2.76(1H,m); 3.63(2H,m); 4.69(1H,dd); 7.04(2H,s); 7.60(1H,t); 8.0(1H,bs). (This material can be contaminated by varying amounts of the 2-chloro analogue). Base-catalysed cyclisation of this material (2.46g) gave the 3-bromopyrrolidinone (1.66g). NMR ($CDCl_3$): δ 2.51(1H,m); 2.76(1H,m); 3.81(1H,dt); 4.04(1H,m); 4.59(1H,dd); 7.06(1H,d); 7.17(1H,dd); 7.68(1H,d). MS: M^+ 319, 321). (This material can be contaminated by varying amounts of the 3-chloro analogue). Treatment of the bromide (1.66g) with sodium iodide in acetone gave the iodopyrrolidinone (1.82g, m.p. 71-74°C). NMR ($CDCl_3$): δ 2.39(1H,m); 2.62(1H,m); 3.71(1H,dt); 3.92(1H,m); 4.72(1H,dd); 7.05(1H,d); 7.16(1H,dd); 7.67(1H,d). MS: M^+ 367. Further treatment of this material (1.0g) with gaseous methylamine in tetrahydrofuran gave the 3-methylaminopyrrolidinone (0.74g, m.p. 65-69°C). NMR ($CDCl_3$): δ 1.98(1H,m); 2.49(1H,m); 2.53(3H,s); 2.81(1H,d); 3.53(1H,dd); 3.77(2H,m); 7.03(1H,d); 7.12(1H,dd); 7.68(1H,d). MS: M^+ 270.

Samples of this amine (0.20g) were treated with t-butyl isocyanate to give Compound 194 (0.22g, m.p. 155-157°C) and with 3,3-dimethylbutanoyl chloride to give Compound 195 (0.16g, m.p. 111-112°C). Compound 194 had NMR ($CDCl_3$): δ 1.37(9H,s); 2.13(1H,m); 2.47(1H,m); 2.84(3H,s); 3.75(2H,m);

4.44(1H,bs); 5.17(1H,dd); 7.04(1H,d); 7.12(1H,dd); 7.73(1H,d). MS: M^+ 369. Compound 195 had NMR ($CDCl_3$): δ 1.09(9H,s); 2.20(1H,d); 2.33(2H,d); 2.44(1H,m); 2.88(0.3H,s); 3.07(2.7H,s); 3.80(2H,m); 5.14(1H,t); 7.03(1H,d); 7.12(1H,dd); 7.71(1H,d). This spectrum is complicated by effects arising from restricted rotation. MS: M+ 368.

EXAMPLE 71 **Preparation of Compound 196: 3-t-Butylcarbamoyloxy-1(2-chlorothien-5-yl)pyrrolidin-2-one**

The title compound was prepared by procedures similar to those described in Example 50.
5-Bromo-2-chlorothiophene (15.8g) was treated with pyrrolidin-2-one and cuprous oxide to give 1(2-chlorothien-5-yl)pyrrolidin-2-one (3.25g, m.p. 152-154°C). NMR ($CDCl_3$): δ 2.25(2H,m); 2.63(2H,m); 3.83(2H,t); 6.21(1H,d); 6.70(1H,d). Oxidation of this material (3.25g) gave the corresponding 3-hydroxypyrrolidin-2-one (0.34g, m.p. 159-161°C). NMR ($CDCl_3$): δ 2.20(1H,m); 2.65(1H,m); 3.70(1H,m); 3.87(1H,m); 3.0(1H,bs); 4.55(1H,t); 6.30(1H,d); 6.72(1H,d). MS: M^+ 217, 219. Treatment of this material (0.20g) with t-butylisocyanate gave Compound 196 (0.04g, m.p. 177-179°C). NMR ($CDCl_3$): δ 1.37(9H,s); 2.20(1H,m); 2.78(1H,m); 3.75(1H,m); 3.87(1H,m); 4.87(1H,bs); 5.40(1H,t); 6.30(1H,d); 6.72(1H,d). MS: M^+ 316, 318.

EXAMPLE 72 **Preparation of Compound 197: 3-(N,N-diisopropylcarbamoyl)-amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone.**

3-Amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (0.305g), prepared in a similar manner to that described in Step 4 of Example 1, diisopropyl-carbamoylchloride (0.409g), and 4-N,N-dimethylaminopyridine (0.152g) were dissolved in DMF (2ml) and stirred at room temperature for 3 days. The reaction mixture was then poured into water and extracted into ethyl acetate (3 times). The combined ethyl acetate extracts were washed with water (twice) before drying ($MgSO_4$) and concentrating to an oil. Column chromatography eluting with ethyl acetate / hexanes (2:1) gave the product as a gum (0.09g, 19%).

EXAMPLE 73 **Preparation of Compound 198: 3-(N-methyl,N-t-butylcarbamoyl)-amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone.**

1-(3-Trifluoromethoxy)phenyl-2-pyrrolidinone-3-carboxylic acid (0.5g), prepared as described in Example 7, Step 1, and triethylamine (0.24ml) were dissolved in toluene (10ml). Diphenylphosphoryl azide (0.384ml) was then added and the mixture heated to 90-100°C for 1.25 hours. Nitrogen gas was evolved during the first 15 mins. The reaction mixture was then allowed to cool to room temperature, t-Butylmethylamine (0.2ml) was added and the reaction stirred at room temperature for 1.5 hours. During this time a white precipitate formed which was filtered off. t-Butylmethylamine (0.4ml) was added to the toluene solution and the reaction mixture heated to 70°C for 7 hours before allowing to cool overnight. The mixture was then poured into water and extracted into ethyl acetate 3 times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the crude product. Column chromatography eluting with ethyl acetate / hexanes 1:1 gave the product as a white powder (150mg, 23%). M.p. 136 - 138°C

EXAMPLE 74 **Preparation of Compound 234: 3-((N-ethyl)dimethylaminoacetyl) amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone**

A solution of 3-(N-ethyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone (0.105 g) in dichloromethane (10 ml) was treated with chloroacetyl chloride (0.031ml) and left to stand for 1 hour. The solution was then washed with dilute hydrochloric acid followed by saturated sodium bicarbonate, then dried ($MgSO_4$) and evaporated under reduced pressure. The residue, which contained crude 3-((N-ethyl)chloroacetyl)amino-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone, was dissolved in tetrahydrofuran (10 ml) and treated with a 40% aqueous solution of dimethylamine (2 ml) together with sodium iodide (ca. 5mg). The resultant mixture was stirred at room temperature for 2 hours, then water was added, and the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried (MgSO4) and evaporated under reduced pressure, to leave the title compound (0.065 g).

EXAMPLE 75 **Preparation of Compounds 235, 236 237 and 238**

A stirred solution of Compound 53 (0.200 g) (prepared by a method similar to that described in Example 1) in toluene (10 ml) was treated with glyoxylic acid monohydrate (0.042 g) and the mixture was heated under reflux for 4 hours, with the water produced being removed using a Dean and Stark trap. The resultant solution was evaporated under reduced pressure to dryness, and the residue was separated by chromatography on silica gel, eluting with ethyl acetate/hexane mixtures, to afford each of the title compounds in a pure state. Compounds 234 and 235 are diastereomers, as are Compounds 236 and 277.

EXAMPLE 76 **Preparation of Compound 239: N-(1,1-dimethylpropargyl) [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetamide**

Step 1 Preparation of Benzyl [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetate

A solution of methyl [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl] acetate (prepared by a method similar to that described in Example 15) (0.719 g) in benzyl alcohol (10 ml) was treated with 1 drop of concentrated sulfuric acid, and stirred for 48 hours, after which time gas chromatrography indicated that the reaction had gone to 2% completion. A further drop of concentrated sulfuric acid was added, and the mixture was stirred for a further 13 days, when gas chromatography indicated that the reaction had gone to 86% completion. The mixture was diluted with diethyl ether, and the solution was washed with water, dried (MgSO4) and evaporated under reduced pressure to leave a colourless liquid, which contained benzyl alcohol. Kugelrohr distillation at 100°C at 0.01 mm Hg removed the benzyl alcohol, leaving the crude title compound as a clear liquid, which contained ca. 12% of the methyl ester starting material. This was used in the next step without further purification.

Step 2 Preparation of [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetic acid

A solution of benzyl 2-[3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetate from Step 1 (0.750g) in ethanol (8 ml) containing trifluoroacetic acid (5 drops) was hydrogenated over a 5% palladium on charcoal catalyst for 29 hours, and the mixture was then filtered through Hyflo (washing through with ethanol). The filtrate was evaporated under reduced pressure to give a brown oil, which was purified by chromatography over silica-gel, eluting with a 60:40 mixture of hexane/ethyl acetate, to afford the title compound as a white solid (0.300g).

Step 3 Preparation of [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetyl chloride

A stirred suspension of [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetic acid from Step 2 above (0.290 g) in carbon tetrachloride (3 ml) was treated with oxalyl chloride (0.130 g), and the mixture was heated under gentle reflux for 2 hours. The resultant colourless solution was cooled and evaporated under reduced pressure to leave the title compound (0.295 g).

Step 4 Preparation of N-(1,1-dimethylpropargyl) [3-(3-trifluoromethoxy) phenyl-4-oxazolidinone-5-yl]acetamide

A stirred solution of 1,1-dimethylpropargylamine (131 mg) in diethyl ether (1 ml) was treated with a solution of [3-(3-trifluoromethoxy)phenyl-4-oxazolidinone-5-yl]acetyl chloride from Step 3 above (0.220 g), and the resultant suspension was stirred for a further 1 hour. The mixture was filtered, and the filtrate was evaporated under reduced pressure to leave the crude title compound as a white solid. This was purified by preparative thin layer chromatography, eluting with ethyl acetate/hexane (1:1), to afford the pure title compound as a white solid (0.214 g).

EXAMPLE 77 **Preparation of Compound 244: N-(t-butyl)[3-(3-trifluoromethyl-4-fluoro)phenyl-4-oxazolidonone-5-yl]acetamide**

Step 1 preparation of the ethyl ester of N-(3-trifluoromethyl-4-fluoro)phenyl fumaric acid amide

A stirred solution of 3-trifluoromethyl-4-fluoroaniline (21.10 g) and monoethyl fumarate (17.90 g) in tetrahydrofuran (100 ml) was treated slowly with a solution of dicyclohexyl carbodiimide (24.30 g) in tetrahydrofuran (50 ml). The resultant thick white suspension was stirred for a further 1 hour, and was then filtered. The filtrate was evaporated under reduced pressure, the residue was triturated with hexane, and the white precipitate was filtered off, washed with hexane, and dried, affording the title compound as a white solid (18.70 g). A further 6.30 g of this compound was obtained by concentration of the mother liquors from the trituration under reduced pressure.

Step 2 Preparation of N-(3-trifluoromethyl-4-fluoro)phenyl fumaric acid amide

A stirred slurry of the ethyl ester from Step 1 above (23.50 g) in ethanol (80 ml) was treated with a solution of sodium hydroxide (3.10 g) in water (20 ml). The mixture was stirred for 30 minutes, acidified to pH 1 using 2M hydrochloric acid. The resultant white precipitate was filtered off, washed with water and dried, affording the title compound as a white solid (20.40g).

Step 3 Preparation of the t-butyl ester of N-(3-trifluoromethyl-4-fluoro)phenyl fumaric acid amide

A suspension of the acid from step 2 (10.00 g) in toluene (150 ml) was stirred at 70°C, and treated dropwise over 30 minutes with dimethyl formamide (bis)-t-butyl acetal (34.5ml). The mixture was allowed to cool and was filtered. The filtrate was washed with water, saturated sodium bicarbonate and brine, dried (MgSO4) and evaporated under reduced pressure to leave a brown solid. This was purified by silica-gel

chromatography, eluting with ethyl acetate/hexane mixtures (1:9), and then recrystallised from carbon tetrachloride to afford the title compound as a white solid (5.00 g).

Step 4 Preparation of t-butyl [3-(3-trifluoromethyl-4-fluoro)phenyl-4-oxazolidinone-5-yl]acetate

A stirred solution of the ester from Step 3 above (4.50 g) in dimethyl formamide (25 ml) was treated with a 80% dispersion of sodium hydride in oil (0.042g), followed by paraformaldehyde (2.10 g). The white suspension was stirred for 1 hour, and the reaction was then quenched by the addition of 2M hydrochloric acid. The resultant mixture was extracted with diethyl ether (2x) and the combined ether extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to leave an off-white solid residue. This was recrystallised from diethyl ether/hexane to afford the title compound (3.70 g) as colourless crystals.

Step 5 Preparation of [3-(3-trifluoromethyl-4-fluoro)phenyl-4-oxazolidinone-5-yl]acetic acid (Compound 243)

The t-butyl ester from Step 4 above (3.60 g) was dissolved in dichloromethane (25 ml) and the solution was treated with trifluoroacetic acid (7.60 ml). The clear solution was stirred for 1 hour, then washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to leave an oil which crystallised on standing. Purification by silica-gel chromatography, eluting with ethyl acetate/hexane (1:1) afforded the title compound as a white solid (3.05 g).

Step 6 Preparation of [3-(3-trifluoromethyl-4-fluoro)phenyl-4-oxazolidinone-5-yl]acetyl chloride

A solution of the acid from Step 5 above (2.60 g) in carbon tetrachloride (10 ml) was treated with oxalyl chloride (2.2 ml). The mixture was then heated under gentle reflux for 1 hour, then cooled and evaporated under reduced pressure to leave the crude title compound as a pale brown oil (2.75 g). This was used in the next stage without further purification.

Step 7 Preparation of N-(t-butyl)[3-(3-trifluoromethyl-4-fluoro)phenyl-4-oxazolidonone-5- yl]acetamide

A solution of the acid chloride from Step 6 above (0.390 g) in diethyl ether (1 ml) was added to a stirred solution of t-butylamine (0.204 g) in diethyl ether (3 ml). The thick suspension was stirred for 1 hour, then water was added and the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and evaporated under reduced pressure to give an off-white solid, which was recrystallised from diethyl ether to afford the title compound as a white solid (0.080 g). The mother liquors from the recrystallisation were evaporated under reduced pressure, and the residue was recrystallised from diethyl ether/hexane to give a further crop of the title compound (0.200 g).

EXAMPLE 78 **Preparation of Compound 253: 3-((N-2-(t-butylcarbamoyloxy) ethyl)- t-butylcarbamoyl)amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone**

A stirred solution of 3-(N-2-hydroxyethyl)amino-1-(3-trifluoromethoxy) phenyl-2-pyrrolidinone (prepared by a method analogous to that described in Example 27, Step 1, but using 2-hydroxyethanol in place of allylamine) (0.069 g) in dichloromethane (5 ml) was treated with t-butyl isocyanate (0.022 ml) and triethylamine (0.028 ml), and the resultant solution was stirred for 16 hour. The mixture was then evaporated to dryness, and the residual mixture was separated by silica-gel chromatography, eluting with ethyl acetate/hexane (1:2), to afford the title compound (0.064 g).

EXAMPLE 79 **Preparation of Compound 280: 2-[1-(3-[trifluoromethyl] phenyl)oxazolidin-2-on-3-yl]propanamide, and also of Compounds 278 and 279, the two diastereomers of benzyl 2-[1-(3-[trifluoromethyl]phenyl) oxazolidin-2-on-3-yl]propanoate.**

Step 1

A solution of 3-aminobenzotrifluoride (16.2g) in diethyl ether (50ml) was added dropwise to a stirred solution of citraconic anhydride (11.2g) in dry diethyl ether (75ml) under nitrogen over a period of 30 minutes. During the addition, the temperature was maintained at 15-20 ^{o}C by cooling in an ice-bath. A white precipitate was formed. Following the addition, the reaction mixture was stirred or allowed to stand at room temperature for a total of about 48 hours. The precipitate was then filtered off and air-dried to give (Z)-N-[3-(trifluoromethyl)phenyl]-3- carboxybut-2-enamide (25.6g) as a white powder, m.p. 135-7 ^{o}C, 1H NMR: δ 1.95 (3H, s), 6.05 (1H, s), 7.36 (1H, d), 7.50 (1H, t), 7.68 (1H, d), 8.08 (1H, s), 10.40 (1H, s), 12.80 (1H, br s) ppm.

Step 2

A mixture of the amide from step 1 (5.46g) and diethyl azodicarboxylate (3.48g) in dry THF (80ml) was stirred at room temperature under nitrogen, producing a yellow solution. A solution of triphenylphosphine (5.25g) and methanol (0.64g) in dry THF (40ml) was then added dropwise over a period of 45 minutes (mildly exothermic). Following the addition, the reaction mixture was stirred at room temperature for 4 hours. It was then stripped down under reduced pressure to leave a colourless paste, which was purified by chromatography using a 1 : 1 mixture of ethyl acetate and hexane as eluent to give (Z)-N-[3-(trifluoromethyl)phenyl]-3- (methoxycarbonyl)but-2-enamide (3.29g) as a white, waxy solid, 1H NMR: δ 2.06 (3H, d), 3.86 (3H, s), 6.08 (1H, d), 7.34 (2H, m), 7.75 (1H, d), 7.84 (1H, s), 8.84 (1H, br s) ppm.

Step 3

A mixture of the amide from step 2 (1.60g) and N-bromosuccinimide (99mg) in carbon tetrachloride (30ml) was heated under reflux for 38 hours. Further portions of N-bromosuccinimide (50mg) were added during heating,

after 7 and 14 hours. The volatiles were then removed under reduced pressure, and the residue was chromatographed using a 1 : 1 mixture of ethyl acetate and hexane as eluent to give a pale yellow solid (1.32g), which was combined with material from a parallel reaction on the same scale. The resulting material, a pale yellow solid (2.56g), was shown to contain about 60% (E)-N-[3-(trifluoromethyl)phenyl]-3-(methoxycarbonyl)but-2-enamide. This impure material was used directly in step 4.

Step 4

Aqueous sodium hydroxide (50ml, 2M solution) was added to a stirred solution of the crude amide from step 3 (2.56g) in tetrahydrofuran (75ml), producing a deep purple solution. After about 2 hours, the reaction mixture was poured into water. The resulting mixture was washed with ethyl acetate, acidified with concentrated hydrochloric acid, and then extracted with dichloromethane. The dichloromethane extracts were washed with water and dried. Removal of the solvent under reduced pressure then gave a sticky solid which, on trituration with diethyl ether, yielded a pale cream-coloured powder (1.30g). Analysis by proton NMR showed that this powder was a ca. 2 : 1 mixture of the (E)- and (Z)-isomers of N-[3-(trifluoromethyl)phenyl]-3-carboxybut-2-enamide.

Step 5

The amide from step 4 (1.28g) and diethyl azodicarboxylate (0.817g) were stirred as a mixture in dry THF (40ml) under nitrogen. A solution of triphenylphosphine (1.23g) and benzyl alcohol (0.507g) in dry THF (20ml) was added dropwise over 10 minutes (mild exotherm). An hour later, the solvent was stripped off under reduced pressure and the residue was triturated with diethyl ether. The insoluble material, which was 1,2-dicarbethoxyhydrazine (0.52g), was discarded. The soluble material was chromatographed using a 1 : 2 mixture of ethyl acetate and hexane as eluent to give (E)-N-[3-(trifluoromethyl)phenyl]-3-(benzyloxycarbonyl)but-2-enamide (0.697g) as a white powder, m.p. 116-8 ^{o}C, 1H NMR: δ 2.40 (3H, d), 5.27 (2H, s), 6.94 (1H, d), 7.40 (7H, m), 7.70 (2H, m), 7.89 (1H, s) ppm.

Step 6

A solution of the amide from step 5 (0.636g) in dry DMF (10ml) was added dropwise over 10 minutes to a stirred suspension of sodium hydride (7mg of a 60% oil dispersion) in dry DMF (10ml) under nitrogen. The reaction mixture turned dark red. After 5 minutes, paraformaldehyde (0.263g) was added as a solid in one portion, and the resulting mixture was stirred at room temperature for 2 hours, during which time the colour faded. The reaction mixture was poured into water (50ml) containing 2M hydrochloric acid (2ml), and this aqueous mixture was then extracted with diethyl ether. The extracts were washed with brine, dried, concentrated and chromatographed using a 1 : 3 mixture of ethyl acetate and hexane as eluent to give a roughly 1 : 1 mixture of diastereomers of benzyl 2-[1-(3-[trifluoromethyl]phenyl)oxazolidin-2-on-3-yl]propanoate (0.356g) as a viscous colourless oil. HPLC on Sorbsil C30™ silica gel using a 1 : 5 mixture of ethyl acetate and hexane as eluent then separated these diastereomeric products (the configurations of these products were not assigned). Diastereomer A, eluted first, was a viscous, colourless gum (0.107g), 1H NMR as in Table III; diastereomer B, eluted second, was a white powder (0.118g), 1H NMR as in Table III.

Step 7

Trifluoroacetic acid (1 drop) and 10% palladium on carbon (10mg) were added successively to a stirred solution of diastereomer A of the propanoate from step 6 (0.105g) in ethyl acetate (15ml). The resulting mixture was treated with hydrogen at atmospheric pressure for 6 hours at room temperature. The atmosphere of hydrogen was then replaced with nitrogen, and the reaction mixture was allowed to stand overnight and was then filtered through 'Hyflo'™. The filtrate was concentrated to leave a single diastereomer of 2-[1-(3-[trifluoromethyl]phenyl)oxazolidin-2-on-3-yl]propanoic acid as a white solid (73mg), 1H NMR: δ 1.33 (3H, d), 3.17 (1H, m), 4.92 (1H, m), 5.54 (2H, s), 7.52 (2H, m), 7.80 (2H, m) ppm.

Step 8

A mixture of the propanoic acid from step 7 (72mg) and oxalyl chloride (5ml) was stirred at room temperature for 1 hour, then all the volatiles were stripped off under reduced pressure. The residue was taken up in dry dichloromethane (8ml) and stirred under nitrogen, and a solution of t-butylamine (17mg) and triethylamine (26mg) in dry dichloromethane (2ml) was added dropwise over 2 minutes (white fumes and mild exotherm). The resulting mixture was stirred at room temperature for 3.5 hours, then washed with water, dried, concentrated and chromatographed using a 1 : 1 mixture of ethyl acetate and hexane as eluent to give a single diastereomer of N-t-butyl-[1-(3-[trifluoromethyl] phenyl)oxazolidin-2-on-3-yl]propanamide, containing small amounts of the starting acid and its corresponding anhydride, as a colourless gum (46mg). After this sample had been allowed to stand for a week, analysis showed that the anhydride had gone, presumably having been hydrolysed to the acid. The sample then comprised the single diastereomer of N-t-butyl 2-[1-(3-[trifluoromethyl]phenyl)oxazolidin-2-on-3-yl]propanamide containing about 25% of the starting acid. This material was a solid, with 1H NMR for the amide as shown in Table III.

EXAMPLE 80 **Preparation of Compound 285: N-[pyrid-2-ylmethyl]-N-[1-(3-[trifluoromethyl]phenyl)pyrrolidin-2-on-3-yl]-3,3-dimethylbutanamide.**

Step 1

Bromine (4.3ml) was added over a period of 30 minutes, below the surface of the reaction mixture, to a stirred mixture of gamma-butyrolactone (8.60g) and phosphorus tribromide (0.2ml), heating the reaction mixture throughout to a temperature between 100 and 110 ^{o}C. Following the addition, the mixture was heated with stirring at 100^{o}C for 2 hours, then allowed to cool to 50 ^{o}C. Dry DMF (0.01ml) was added, the mixture was heated to 90 ^{o}C, thionyl chloride (8.6ml) was added dropwise over 20 minutes (effervescence), and the resulting mixture was heated at 100^{o}C for a further 3 hours. After cooling, the reaction mixture was subjected to short-path distillation (Kugelrohr), and all material which distilled at less than 80^{o}C at 1-2 mbar was collected. This distillate was

a dark yellow oil (17.5g), containing roughly 50% (by 1H NMR) 2,4-dibromobutanoyl chloride. This crude material was used directly for step 2.

Step 2

A solution of 3-aminobenzotrifluoride (5.32g) and triethylamine (3.67g) in dry THF (50ml) was added dropwise over 30 minutes to a solution of the crude acid chloride from step 1 (17.5g) in dry THF (75ml), cooled in an ice-water bath to keep the temperature below 10°C (a precipitate was formed). The resulting mixture was allowed to warm to room temperature, and it was then stirred for 5 hours and allowed to stand overnight. The mixture was poured into 1M hydrochloric acid (100ml), and then extracted with ethyl acetate. The extracts were washed with brine, dried, concentrated, then chromatographed using a 1 : 3 mixture of ethyl acetate and hexane as eluent to give almost pure N-[3-(trifluoromethyl)phenyl]-2,4-dibromobutanamide as a very pale brown solid (11.95g). 1H NMR: δ 2.57 (1H, m), 2.73 (1H, m), 3.59 (2H, m), 4.70 (1H, dd), 7.46 (2H, m), 7.73 (1H, m), 7.85 (1H, s), 8.23 (1H, br s) ppm.

Step 3

Sodium hydride (1.2g of a 60% dispersion in oil) was added in portions over 10 minutes to a stirred solution of the amide from step 2 (11.67g) in dry THF (150ml) under nitrogen (effervescence and mild exotherm). The resulting mixture was stirred at room temperature for 4 hours, then further sodium hydride (0.25g of a 60% dispersion in oil) was added, and the mixture was stirred for a further 2 hours. Water was carefully added to the reaction mixture, and it was extracted with ethyl acetate. The extracts were washed with brine, dried, filtered and chromatographed using a 1 : 3 mixture of ethyl acetate and hexane as eluent to give 3-bromo-1-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one (5.70g) as a white powder. 1H NMR: δ 2.48 (1H, m), 2.78 (1H, m), 3.87 (1H, m), 4.08 (1H, m), 4.60 (1H, m), 7.48 (2H, m), 7.90 (2H, m) ppm.

Step 4

A solution of 2-(aminomethyl)pyridine (1.95g) and triethylamine (0.91g) in dry THF (25ml) was added dropwise over 1 hour to a stirred

solution of the bromopyrrolidinone from step 3 (0.924g) in dry refluxing THF (25ml) under nitrogen. The reaction mixture was then heated under reflux for 24 hours and allowed to cool. The solvent was stripped off under reduced pressure, and the residue was taken up in ethyl acetate, washed with water, dried, concentrated under reduced pressure, and chromatographed using a 9 : 1 mixture of chloroform and ethanol as eluent to give 3-(pyrid-2-ylmethylamino)-1-[3-(trifluoromethyl)phenyl] pyrrolidin-2-one as a mobile yellow oil (1.08g) which set to a waxy solid, m.p. 82-3 ^{o}C, on standing. 1H NMR: δ 2.05 (1H, m), 2.50 (2H, m), 3.70 (1H, dd), 3.84 (2H, m), 4.10 (2H, 'AB quartet'), 7.19 (1H, m), 7.40 (2H, m), 7.49 (1H, m), 7.69 (1H, dt), 7.90 (2H, m), 8.58 (1H, m) ppm.

Step 5

A solution of the aminopyrrolidinone from step 4 (0.335g) and triethylamine (0.111g) in dry dichloromethane (6ml) was added dropwise over 10 minutes to a stirred solution of 3,3-dimethylbutanoyl chloride (0.148g) in dry dichloromethane (2ml) at room temperature under nitrogen (white fumes and exotherm). The resulting mixture was stirred for 7 hours and allowed to stand overnight. It was then washed with water, dried, concentrated and chromatographed using a 9 : 1 mixture of ethyl acetate and ethanol as eluent to give N-[pyrid-2-ylmethyl]-N-[1-(3-[trifluoromethyl]phenyl)pyrrolidin-2-on-3-yl]-3,3-dimethylbutanamide as a pale yellow gum (0.355g), with 1H NMR as in Table III.

The following compounds were prepared from 3-bromo-1-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one (the product of step 3) using analogous routes: Compounds 287, 289 and 283.

EXAMPLE 81 **Preparation of Compound 286: N-[pyrid-2-ylmethyl]-N-[1-(3-[trifluoromethyl]phenyl)pyrrolidin-2-on-3-yl]-N'-[t-butyl]urea**

Step 1

t-Butyl isocyanate (0.297g) was added to a stirred solution of 3-(pyrid-2-ylmethylamino)-1-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one (0.335g, prepared as described in Example 80) and triethylamine (0.304g) in dry dichloromethane (8ml) under nitrogen. The resulting mixture was then

stirred for 7 hours, and allowed to stand overnight. The volatiles were stripped off under reduced pressure, and the residue was purified by chromatography, using a 9 : 1 mixture of ethyl acetate and ethanol as eluent, to give N-[pyrid-2-ylmethyl]-N-[1-(3-[trifluoromethyl]phenyl) pyrrolidin-2-on-3-yl]-N'-[t-butyl]urea as a white powder (0.290g), m.p. 147-9°C, with 1H NMR data as in Table III. The following compounds were prepared by analogous methods: Compounds 288, 290 and 284.

EXAMPLE 82 **Preparation of Compound 281: N-[methyl]-N-[1-(3-[trifluoromethoxy]phenyl)pyrrolidin-2-on-3-yl]-N'-[2-(trifluoromethyl)prop-2-yl]urea**

Step 1

A solution of phosgene in toluene (4.0ml of a 1.93M solution) was added to 2-(trifluoromethyl)prop-2-ylamine hydrochloride (0.420g, prepared from 2-aminoisobutyric acid according to the procedure described in J. Organic Chem., (1961), 27, 1406) in toluene (4.0ml), and the resulting mixture was heated with stirring at 60°C for 2 hours. Most of the solid amine hydrochloride dissolved during this time. The mixture was allowed to cool to room temperature and the excess phosgene was removed under reduced pressure. 3-(Methylamino)-1-[3-(trifluoromethoxy)phenyl]pyrrolidin-2-one (0.50g, prepared in analogy to the procedure for the preparation of 3-(Methylamino)-1-[3-(trifluoromethyl)phenyl] pyrrolidin-2-one described in Example 10) and triethylamine (0.185g) were then added successively with stirring, and the mixture was stirred for 4 hours at room temperature and allowed to stand overnight. The reaction mixture was applied to the top of a column of silica gel, and eluted with a 7 : 3 mixture of ethyl acetate and hexane to give N-[methyl]-N-[1-(3-[trifluoromethoxy]phenyl)pyrrolidin-2-on-3-yl]-N'-[2-(trifluoromethyl) prop-2-yl]urea as a white solid (0.220g), m.p. 115-6 °C, with 1H NMR data as in Table III.

EXAMPLE 83 **Preparation of Compound 301: N-(propargyl)-N-[3-(3-trifluoromethyl)phenylthiazolidin-4-on-5-yl]-N'-(neopentyl)urea**

Step 1

Propargylamine (4.061g) was added to a stirred solution of 5-chloro-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one (5.196g, prepared as described in Example 1); the reaction mixture darkened, and a thick precipitate formed. The mixture was stirred for 9 hours and the volatiles were stripped off under reduced pressure. The residue was taken up in t-butyl methyl ether (orange solution plus solid) and washed successively with water (x3) and brine, then dried, concentrated and chromatographed to give 5-propargylamino-3-[3-(trifluoromethyl)phenyl] thiazolidin-4-one as a viscous brown oil (3.720g), 1H NMR: δ 2.28 (2H, m), 3.66 (2H, dd), 4.77 (1H, d), 4.88 (1H, d), 5.19 (1H, s), 7.50 (2H, m), 7.75 (2H, m) ppm.

Step 2

A mixture of 3,3-dimethylbutanoic acid (0.577g), diphenylphosphoryl azide (1,369g) and triethylamine (0.503g) in dry toluene (15ml) was heated with stirring at about 80 °C under nitrogen for 2 hours. Effervescence began to occur after about 20 minutes, and had ceased after 2 hours. The mixture was allowed to cool to room temperature, and the thiazolidinone from step 1 (0.500g) and triethylamine (0.167g) were added with stirring. The following morning, the solvent was removed under reduced pressure, and the residue was chromatographed using a 3 : 2 mixture of hexane and ethyl acetate as eluent to give N-(propargyl)-N-[3-(3-trifluoromethyl)phenylthiazolidin-4-on-5-yl]-N'-(neopentyl)urea as a solid (0.484g), almost pure by NMR spectroscopy. Recrystallisation from a mixture of ethyl acetate and hexane gave the product as a yellow crystalline solid (0.267g), m.p. 145-145.5°C, with 1H NMR data as in Table III.

The urea Compound 302 was prepared from 5-propargylamino-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one, the product of step 1 above, and 3-chloro-2,2-dimethylpropanoic acid in the same way. The urea, Compound

298 was made from 5-propargylamino-3-[3-(trifluoromethyl) phenyl]thiazolidin-4-one and the available t-butyl isocyanate using the method described for a related pyrrolidinone in Example 27. The amide Compound 297 was prepared from 5-propargylamino-3-[3-(trifluoromethyl) phenyl]thiazolidin-4-one and 3,3-dimethylbutanoyl chloride by a conventional method similar to that described for related compounds in Examples 3 and 25.

The following ureas and amides were prepared from 5-chloro-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one using appropriate amines and then isocyanates (either directly or produced in situ by the Curtius rearrangement of appropriate acids using the method described above) or acid chlorides according to the steps described above: Compounds 124, 125, 291, 292, 293, 294, 295, 296 and 300.

EXAMPLE 84 **Preparation of Compound 299: N-(methoxy)-N-[3-(3-trifluoromethyl)phenylthiazolidin-4-on-5-yl]-N'-(t-butyl)urea**

Step 1

A viscous mixture of methoxylamine hydrochloride (1.482g) and triethylamine (1.793g) in DMF (10ml) was stirred at room temperature for 5 minutes. 5-Chloro-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one (1.000g, prepared as described in Example 1) was added, and the mixture turned pink. It was stirred for 3 hours, then diluted with water and extracted with diethyl ether. The extracts were washed with water and then brine, dried, concentrated and chromatographed using a 1 : 1 mixture of ethyl acetate and hexane as eluent to give a dark oil (0.579g) containing 5-methoxyamino-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one. This oil was then combined with similar material from a second experiment which had been performed on 4 x the scale described above. Further chromatography using the same eluent then gave a roughly 1.1 : 1 mixture of 5-methoxyamino-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one and 5-hydroxy-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one as a yellow oil (3.542g); this was treated without further purification with t-butyl isocyanate and triethylamine in dichloromethane in the way described in

Example 81 above to give a 35% yield of N-[methoxy]-N-[3-(3-[trifluoromethyl]phenyl)thiazolidin-4-on-5-yl]-N'-[t-butyl]urea as a white solid, m.p. 128.5-129.5°C, and 1H NMR data as in Table III.

The amide, Compound 126, was prepared from 5-methoxyamino-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one and 3,3-dimethylbutanoic acid and triethylamine using a conventional method similar to that described for related compounds in Examples 3 and 25.

EXAMPLE 85 **Preparation of Compound 303: 3-t-butyl-1-{[3-(trifluoromethyl)phenyl]thiazolidin-4-on-5-yl}-imidazolidin-2,4-dione**

Step 1

Triethylamine (1.974g) was added to a stirred solution of 5-chloro-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one (2.500g, prepared as described in Example 1) and the hydrochloride salt of the methyl ester of glycine (1.336g) in THF (30ml). The reaction mixture, which became bright yellow, was stirred or allowed to stand for a total of about a week. The solvent was then removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and then brine, dried, concentrated and chromatographed using a 2 : 3 mixture of hexane and ethyl acetate as eluent to give 5-[(methoxycarbonyl)methylamino]-3-[3-(trifluoromethyl) phenyl]thiazolidin-4-one as a yellow solid (1.014g), 1H NMR: δ 2.60 (1H, s), 3.56 (1H, d), 3.69 (1H, d), 3.75 (3H, s), 4.75 (1H, d), 4.82 (1H, dd), 5.19 (1H, s), 7.55 (2H, m), 7.72 (2H, m) ppm.

Step 2

Triethylamine (0.293g) and t-butyl isocyanate (0.287g) were added to a stirred solution of the thiazolidinone from step 1 (0.970g) in dichloromethane. The resulting mixture was either stirred or allowed to stand at room temperature for a total of about 6 days. The solvent was then removed and toluene was added to the residue. The mixture was then heated at 80°C under nitrogen for a total of 8 hours, with intervening periods at room temperature. Extensive chromatography and HPLC, using

mixtures of ethyl acetate and hexane or t-butyl methyl ether and hexane as eluents, followed by crystallisation and recrystallisation from mixtures of ethyl acetate and hexane, then gave 3-t-butyl-1-{[3-(trifluoromethyl)phenyl]thiazolidin-4-on-5-yl}-imidazolidin-2,4-dione as a white crystalline solid (56mg), m.p. 199.5-201°C, with 1H NMR data as in Table III.

EXAMPLE 86 **Preparation of Compound 304: 5-(t-butylaminocarbonylthio)-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one**

Step 1

A mixture of 5-chloro-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one (5.000g, prepared as described in Example 1) and potassium thioacetate (2.227g) were stirred together in DMF (50ml) (mild exotherm on mixing, and mixture became dark brown). After about an hour, the mixture was diluted with water and extracted with diethyl ether. The extracts were washed successively with water and brine, then dried, concentrated and chromatographed using a 2 : 1 mixture of hexane and ethyl acetate as eluent to give 5-acetylthio-3-[3-(trifluoromethyl)phenyl]thiazolidin- 4-one as a dark oil (5.423g), 1H NMR: δ 2.41 (3H, s), 4.79 (1H, d), 5.04 (1H, dd), 5.49 (1H, d), 7.51- 7.77 (4H, m) ppm.

Step 2

Gaseous ammonia was bubbled for 15 minutes through a stirred solution of 5-acetylthio-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one (1.300g) in methanol (15ml), cooled in an ice bath. The reaction mixture was then allowed to warm to room temperature and stir for a further 3 hours. Volatiles were removed under reduced pressure and the residue was chromatographed using a 1 : 1 mixture of ethyl acetate and hexane as eluent to give a roughly 7 : 3 mixture of 5-mercapto-3-[3-(trifluoromethyl) phenyl]thiazolidin-4-one and the corresponding dimeric disulfide, respectively, as a viscous yellow oil (0.976g). This was used without further purification.

Step 3

t-Butyl isocyanate (0.291g) and triethylamine (0.247g) were added successively to a stirred solution of the crude thiol from step 2 (0.683g) in dichloromethane (7ml), and the mixture darkened to an orange colour. After 40 minutes, the reaction mixture was applied to a column of silica gel and eluted with a 1 : 1 mixture of t-butyl methyl ether and hexane to give 5-(t-butylaminocarbonylthio)-3-[3-(trifluoromethyl) phenyl]thiazolidin-4-one as a yellow solid (0.531g) containing as an impurity roughly 20% N,N'-di-t-butylurea. Recrystallisation from a mixture of ethyl acetate and hexane gave 5-(t-butylaminocarbonylthio)-3-[3-(trifluoromethyl)phenyl]thiazolidin-4-one as a yellow crystalline solid (0.239g), m.p.149.6-150.6°C, with 1H NMR data as in Table III.

EXAMPLE 87 **Preparation of Compound 328: 3-(4,4,4-Trifluorobutanoyl-N-methyl)amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone**

4,4,4-trifluorobutyric acid (0.31g) was dissolved in CH_2Cl_2 (10mls), cooled in an ice/water bath and stirred under a nitrogen atmosphere. To this was added triethylamine (0.31mls) then pivaloylchloride (0.27ml) dropwise. Stirring was continued for 60 minutes. A fine white needle precipitate formed over this time. A solution of the amino pyrrolidinone (prepared in a similar manner to that described in Step 2 of Example 10) (0.4g), DMAP (50mg) and triethylamine (0.2ml) in CH_2Cl_2 (10mls) was added to the cooled reaction mixture. After 30 minutes at this temperature, the reaction was allowed to warm to room temperature and stirred for 60 minutes. The mixture was diluted with CH_2Cl_2, washed with 2N HCl (aq) (x2), brine (x2), dried ($MgSO_4$), filtered and evaporated. Chromatography on silica gave the amide as a gum (0.543g).

EXAMPLE 88 **Preparation of Compound 326: 3-(Pentafluoropropanoyl-N-methyl)amino-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone**

The amino-pyrrolidone (prepared in a similar manner to that described in Step 2 of Example 10) (0.4g) was dissolved in CH_2Cl_2 (20ml). To this was added DMAP (50mg) and triethylamine (0.21ml) with the reaction cooled

in an ice-water bath. Pentafluoropropionic anhydride (0.3ml) was added dropwise and the mixture stirred for 40 minutes with cooling. The mixture was diluted with CH_2Cl_2, washed with 2N HCl (aq), brine (x1), dried ($MgSO_4$), filtered and concentrated. Purification of the residue by chromatography on silica gave the amide as a solid (0.5g). m.p. 65.5-67.5°C.

EXAMPLE 89 **Preparation of Compound 311: 3-(3-t-Butylimidazoline-2,4-dione-1-yl)-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone**

A solution of Compound 130 (prepared as described in Example 31) (0.523g) in ethylacetate (30ml) containing 10% Pd/C (100mg) was stirred under an atmosphere of hydrogen at room temperature. After 21 hours, the catalyst was filtered and solvent evaporated. Analysis of the residue showed that the reaction was only 40% complete. The residue was re-dissolved in ethylacetate and 50mg of 10% Pd/C added. Hydrogenation was achieved at 3 bar pressure using a hydrogenator for six hours. The catalyst was filtered off and the filtrate evaporated. This process was repeated, except using a pressure of 4 bar hydrogen for 4 hours. After filtering the catalyst and evaporation of solvent, the residue was purified using chromatography on silica, eluting with 60% ethyl acetate in hexane, to give the reduced product as a colourless solid (0.385g) m.p 153-154°C.

EXAMPLE 90 **Preparation of Compound 308: 3-(2,2,2-Trichloroethoxycarbonyl-N-methyl)amino-1(3-trifluoromethyl)phenyl-2-pyrrolidinone**

To a solution of the amino-pyrrolidinone (prepared as described in Step 2 of Example 10) (0.138g) in CH_2Cl_2 (5ml) at 0°C (ice/water bath cooling) was added triethylamine (0.096ml) followed by 2,2,2-trichloroethylchloroformate (0.088ml). The clear solution was stirred at 0°C for 1 hour. The mixture was diluted with CH_2Cl_2, washed with water and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography on silica gave the carbamate as a colourless gum (0.20g).

EXAMPLE 91 **Preparation of Compound 267: 5-(3-allyl-1-t-butyl-3-ureido)-3-(3-trifluoromethylphenyl)oxazolidin-4-one.**

Step 1 Preparation of 2-(methylthio)-N-(3-trifluoromethylphenyl)acetamide

3-Trifluoromethylaniline (16.1g) was added dropwise to a rapidly stirred suspension of hexane-washed sodium hydride (4.0g, 60% in mineral oil) in dimethylsulphoxide (50ml) under a nitrogen atmosphere, with water bath cooling to 20°C. After 30 minutes ethyl (methylthio)acetate (14.7g) was added dropwise with cooling to 20°C. After stirring for 3 hours half-saturated aqueous potassium dihydrogen phosphate (300ml) was added cautiously with cooling to 20°C. The mixture was extracted with diethyl ether (5x100ml), the extract washed with water (2x50ml), dried over sodium sulphate, filtered and ether evaporated under reduced pressure to leave the crude product as a yellow solid (23.8g). A sample was recrystallised from hexane solution for analysis. m.p. 75-77°C. ^{1}H NMR ($CDCl_3$): δ 2.21(3H,s); 3.38(2H,s); 7.45-7.85(4H,m); 8.85(1H,bs).

Step 2 Preparation of N-(Ethoxymethyl)-N-(3-trifluoromethylphenyl)-2-(methylthio)acetamide

Chloromethyl ethylether (18.1g) was added dropwise, during 20 minutes, to a vigorously stirred mixture of crude product of Step 1 (21.8g) dissolved in dichloromethane (50ml), 52% aqueous sodium hydroxide (34g) and benzyl triethylammonium chloride (0.2g), with water-bath cooling to 20°C. After 30 minutes the mixture was treated with saturated aqueous potassium dihydrogen phosphate until pH 8, at 20°C, extracted with dichloromethane (5x100ml), the extract dried over sodium sulphate, filtered and concentrated under reduced pressure to give the crude product as a yellow oil (27.5g). ^{1}H NMR ($CDCl_3$): δ 1.23(3H,t); 2.21(3H,s); 3.0(2H,s); 3.68(2H,bq); 5.1(2H,s); 7.58(4H,m).

Step 3 Preparation of N-(Ethoxymethyl)-N-(3-trifluoromethyl-phenyl)-2-(methylsulphinyl)acetamide

A solution of sodium periodate (20.5g) in water (190ml) was added dropwise to a stirred solution of crude product of Step 2 in ethanol (850ml) at 5°C. The mixture was allowed to reach 20°C gradually and stirred for 24 hours, than concentrated under reduced pressure. The concentrate was extracted with dichloromethane (500ml), the extract dried over sodium sulphate, filtered and concentrated under reduced pressure to give the crude product as a brown oil (27.5g). ^{1}H NMR ($CDCl_3$): δ 1.24(3H,t); 2.76(3H,s); 3.56(2H,s); 3.67(2H,q); 5.12(2H,s); 7.51-7.69(4H,m).

Step 4 Preparation of 5-Hydroxy-3-(3-trifluoromethyl-phenyl)-oxazolidin-4-one

Trifluoroacetic anhydride (17.6g) was added dropwise to a stirred solution of crude product of Step 3 in tetrahydrofuran (220ml) with water bath cooling to 20°C. After 2 hours the mixture of left to stand for 20 hours. A solution of sodium hydrogen carbonate (14.1g) in water (220ml) was added during 5 minutes with stirring and cooling to 20°C. After 30 minutes the mixture was refluxed for 4½ hours, cooled to 25°C, extracted with dichloromethane (3x300ml), the extract dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a brown oil (21.4g). The brown oil (20.09g) was dissolved in 1,4-dioxane (500ml) and hydrogen chloride gas bubbled in for 3¼ hours, with stirring, at 23°C. The mixture was left in a stoppared flask for 20 hours, concentrated under reduced pressure, dissolved in dichloromethane (400ml), neutralised with a minimum of saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate, filtered and concentrated under reduced pressure to a brown oil (21.9g). The oil was subjected to column chromatography on silica gel, gradient eluting with dichloromethane/t-butyl methylether mixtures to give the crude product as a yellow gum (4.7g). The gum was recrystallised from hexane solution to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 4.43(1H,bs); 5.49(1H,s); 5.68(2H,m); 7.49-7.8(4H,m).

Step 5 Preparation of 5-chloro-3-(3-trifluoromethylphenyl)oxazolidin-4-one

Methanesulphonyl chloride (16mg) was added to a stirred solution of 5-hydroxy-3-(3-trifluoromethylphenyl)oxazolidin-4-one (27mg, from Step 4) in diethyl ether (1ml). After 5 minutes triethylamine (18mg) was added and the mixture stirred for 20 hours. Water (1ml) was added, the mixture extracted with ether (3x5ml), the extract dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the crude product as a yellow oil (22mg). ^{1}H NMR ($CDCl_3$): δ 5.56(1H,d); 5.72(1H,d); 6.3(1H,s); 7.5-7.8(4H,m).

Steps 5 and 6 Preparation of 5-(allylamino)-3-(3-trifluoromethylphenyl)oxazolidin-4-one

Methanesulphonyl chloride (0.9g) dissolved in diethylether (2ml) was added to a stirred solution of 5-hydroxy-3-(3-trifluoromethylphenyl)-oxazolidin-4-one (1.0g, from Step 4) in dichloromethane (6ml). Triethylamine (0.8g) dissolved in ether (2ml) was added and the mixture allowed to exotherm to 35°C. After 2½ hours the mixture was cooled in an ice-water bath and a solution of allylamine (0.92g) in ether (2ml) added dropwise. After 1 hour the mixture was treated with aqueous sodium chloride (20ml), extracted with ether (3x80ml), the extract dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the crude product as a yellow gum (1.3g). ^{1}H NMR ($CDCl_3$): δ 3.49(2H,d); 5.13(1H,dd); 5.21(1H,s); 5.3(1H,m); 5.44(1H,d); 5.48(1H,dd); 5.9(1H,m); 7.5-7.8(4H,m).

Step 7 Preparation of 5-(3-allyl-1-t-butyl-3-ureido)-3-(3-trifluoromethylphenyl)oxazolidin-4-one

A solution of the product of Step 6 (0.43g) in t-butylisocyanate (2ml) was stirred for 2 hours then left for 20 hours. The mixture was concentrated under reduced pressure to give a yellow gum which was subjected to column chromatography on silica gel, eluting with dichloromethane: t-butylmethylether 98:2. This gave a yellow solid which was recrystallised from hexane solution to give the product as a white

solid (0.21g). m.p.149-150°C. ^{1}H NMR ($CDCl_3$): δ 1.31(9H,s); 3.86(2H,m); 4.73(1H,s); 5.32(1H,d); 5.45(1H,d); 5.46(1H,dd); 5.56(1H,t); 5.88(1H,s); 5.95(1H,m); 7.5-7.8(4H,m).

EXAMPLE 92 **Preparation of Compound 266: 5-[N-(N-allyl-2-t-butylacetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one**

Pyridine (0.24g) was added dropwise to a stirred solution of t-butylacetylchloride (0.4g) in dichloromethane (2ml) and the resulting solution added dropwise to a stirred solution of 5-(allylamino)-3-(3-trifluoromethylphenyl)oxazolidin-4-one (0.43g, Example 91 Step 6) in dichloromethane (8ml) at 7°C. After stirring at 7°C for 2 hours aqueous sodium chloride (10ml) was added, the mixture extracted with diethylether (3x50ml), the extract dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a yellow gum. The gum was subjected to column chromatography on silica gel eluting with dichloromethane:t-butyl methylether 99:1 to give a yellow solid which yielded the product as a white solid (.26g) on tritriation with cold hexane. m.p. 92-93°C. ^{1}H NMR ($CDCl_3$): δ 1.07(9H,s); 2.26(2H,q); 4.13(2H,d); 5.32(1H,d); 5.33(1H,s); 5.47(1H,d); 5.48(1H,d); 5.62(1H,s); 5.89(1H,m); 7.4-7.8(4H,m).

A similar method was also used to prepare the compounds listed below.

Compound 269: 5-[N-(2-t-butyl-N-methylacetamido)]-3-(3-trifluoromethoxy phenyl)oxazolidin-4-one;

NMR($CDCl_3$) : δ 1.09(9H,s); 2.32(2H,s); 3.12(3H,s); 5.47(1H,s); 5.58(1H,s); 5.95(1H,bs); 7.03-7.17(1H,m); 7.41-7.48(2H,m); 7.61(1H,s).

MPt : 99.5-102°C.

Compound 272: 5[N-(2-t-butyl-N-ethylacetamido)]-3-(3- trifluoromethoxy phenyl)oxazolidin-4-one;

NMR($CDCl_3$) : δ 1.08(9H,s); 1.32(3H,t); 2.29(2H,d); 3.43-3.64(2H,m); 5.30(1H,bs); 5.45(1H,s); 5.58(1H,bs); 7.0-7.19(1H,m); 7.39-7.45(2H,m); 7.60(1H,bs).

MPt : 95-97°C.

Compound 271: 5-[N-(2-t-butylacetamido)]-3-(3-trifluoromethoxy phenyl)oxazolidin-4-one;

NMR($CDCl_3$) : δ 1.07(9H,s); 2/14(2H,s); 5.45(1H,s); 5.55(2H,m); 6.39(1H,bd); 7.05-7.13(1H,m); 7.38-7.44(2H,m); 7.60(1H,s).

MPt : 145-148°C (dec).

EXAMPLE 93 **Preparation of Compound 265: 5-(3-methyl-1-t-butyl-3-uveido)-3-(3-trifluoromethylphenyl)oxazolidin-4-one**

This compound was prepared by a method analogous to Example 91. m.p. 114-116°C. ^1H NMR ($CDCl_3$): δ 1.37(9H,s); 2.91(3H,s); 4.53(1H,bs); 5.47(1H,t); 5.56(1H,t); 6.08(1H,s); 7.5-7.9(4H,m).

The precursor compound was 5-(methylamino)-3-(3-trifluoromethyl-phenyl)oxazolidin-4-one. ^1H NMR ($CDCl_3$): δ 2.57(3H,m); 5.2(1H,d); 5.46(1H,d); 5.5(1H,dd); 7.5-7.9(4H,m).

EXAMPLE 94 **Preparation of Compound 262: 5-[N-(2-t-butyl-N-methylacetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one**

This compound was prepared by a method analogous to Example 92. m.p. 116-117°C. ^1H NMR ($CDCl_3$): Major rotomer: δ 1.09(9H,s); 2.32(2H,s); 3.13(3H,s); 5.5(1H,d); 5.6(1H,t); 5.9(1H,bs); 7.5-7.8(4H,m). The precursor compound is detailed in Example 92.

EXAMPLE 95 **Preparation of Compound 270: 5-[N-(2-t-butylacetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one**

This compound was prepared by a method analogous to Example 92. m.p. 159-161°C. ^{1}H NMR ($CDCl_3$): δ 1/07(9H,s); 2.14(2H,s); 5.49(1H,d); 5.53(1H,dd); 5.59(1H,t); 6.41(1H,bd); 7.5-7.8(4H,m).

The precursor compound was 5-amino-(3-trifluoromethylphenyl)-oxazolidin-4-one. ^{1}H NMR ($CDCl_3$): δ 2.35(2H,bd); 5.23(1H,t); 5.42(1H,d); 5.49(1H,dd); 7.5-7.8(4H,m).

EXAMPLE 96 **Preparation of Compound 260: 5-[N-(1-methylcyclobutyl)-1-acetamide]3-(3-trifluoromethylphenyl)oxazolidin-4-one**

Step 1 Preparation of (3-trifluoromethylphenylamide)ethyl fumarate.

3-Trifluoromethylaniline (32.2g) and ethyl fumarate (30.32g) were mixed and dissolved in tetrahydrofuran (65ml). A solution of dicyclohexylcarbodimide (041.2g) in tetrahydrofuran (100ml) was then added dropwise. The resultant mixture was left to stand overnight, it was then filtered and the filtrate evaporated under reduced pressure to leave a wet yellow solid which was re-crystallised from ether to give the title compound (33.95g) as a white solid. NMR ($CDCl_3$): δ 1.36(3H,t); 4.20(2H,q); 7.12(1H,d); 7.20(1H,d); 7.42(1H,d); 7.50(1H,t); 7.86(1H,s); 7.95(1H,d); 8.35(1H,bs).

Step 2 Preparation of (3-trifluoromethylphenylamido)fumaric acid

Sodium hydroxide (2.78g) in water (120ml) was added to a solution of (3-trifluoromethylphenylamido)ethyl fumarate (10g as prepared in Step 1) in iso-propanol (180ml). The resultant mixture was left to stand over night then evaporated under reduced pressure. The residue was acidified with hydrochloric acid (2N) and extracted with ether. The extracts were dried over magnesium sulphate and evaporated under reduced pressure to leave the title compound (6.94g) as an off white solid. NMR ($CDCl_3$): δ 6.89(1H,d); 7.20(1H,d); 7.33(1H,d); 7.43(1H,t); 7.92(1H,d); 8.06(1H,s).

Step 3 Preparation of (3-trifluoromethylphenylamido)tert-butoxy carbonyl

N,N-Dimethylformamide di-tert-butyl acetal was added to a suspension of (3,trifluoromethyl phenyl amido)fumaric acid (8.24g as prepared in Step 2) in toluene 50ml at 75°C. The resultant mixture was heated under reflux under N_2 for thirty minutes. It was allowed to cool then was washed with water, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica using hexaneether (2:1) as eluant to give the title compound (5.45g) as a white solid. m.p. 104-5-106.5°C. NMR ($CDCl_3$): δ 1.52(9H,s); 6.90(1H,d); 7.0(1H,d); 7.40(1H,d); 7.46(1H,t); 7.83(1H,d); 7.89(2H,s).

Step 4 Preparation of 5-[methylene tert-butoxy carbonyl]3-trifluoromethylphenyl)oxazolidin-4-one

A solution of (3-trifluoromethylphenyl amido)tert-butoxy carbonyl (5.15g as prepared in Step 3) in dimethylformamide (25ml) was added dropwise to a stirred suspension of sodium hydride (0.065g, 60% dispersion in mineral oil) in dimethyl formamide (10ml). Paraformaldehyde (2.7g) was then added in one portion. After thirty minutes the resultant mixture was poured into water and extracted with ether. The extracts were washed with water and brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (5.49g) as a yellow solid. m.p. 78-81°C. NMR ($CDCl_3$): δ 1.44(9H,s); 2.86(2H,m); 4.75(1H,m); 5.51(1H,s); 7.48(1H,d); 7.55(1H,t); 7.79(1H,d); 7.83(1H,s).

Step 5 Preparation of 5-[Methylene carboxy]-3-(3-trifluoromethylphenyl)-oxazolidin-4-one

Trifluoroacetic acid (10ml) was added to a solution of 5-[methylene tert-butoxy carbonyl]-3-(3-trifluoromethylphenyl)oxazolidin-4-one (4.49g, as prepared in Step 4) in dichloromethane (75ml). The resultant mixture was left to stand over night then poured into water and extracted with ether. The extracts were washed with water, dried over magnesium sulphate

and evaporated under reduced pressure to give the title compound (5.32g) as a brown oil, sufficiently pure to be used in Step 8.

Step 6 Preparation of 1-methylcyclobutyl-1-acetamide

Methylene cyclobutane (10g) was added to a solution of acetonitrile (6.62g), glacial acetic acid (73.5ml) and concentrated sulphuric acid (14.7ml). After one hour the resultant mixture was cooled, diluted with water and made basic by the addition of potassium carbonate, then extracted with ether. The extracts were dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (11.45g) as a mixture of a solid and an oil, sufficiently pure to be used in Step 7. NMR ($CDCl_3$): δ 1.39(3H,s); 1.69-1.82(3H,m); 1.82(3H,s); 2.12-2.30(3H,m); 5.73(1H,bs).

Step 7 Preparation of 1-methylcyclobutyl-1-amino chloride

A solution of 1-methylcyclobutyl-1-acetamide (11.45g as prepared in Step 6) in concentrated sulphuric acid was heated under reflux for fifty five hours. The resultant muxture was allowed to cool and was washed with ether. Theaqueous phase was made strongly basic with 50% sodium hydroxide and extracted with ether. The extracts were dried over potassium hydroxide. Hydrogen chloride (g) was bubbled through the extracts to give the title compound (5.63g) as a white solid. m.p. 247-250°C (dec). NMR ($CDCl_3$): δ 1.34(3H,s); 1.69-1.88(4H,m); 2.12-2.29(2H,m); 8.34(3H,bs).

Step 8 Preparation of 5-[N-(1-methylcyclobutyl)-1-acetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one

Oxalyl chloride (3.5ml) was added to 5-[methylenecarboxy]-3-(3-trifluoromethylphenyl)oxazolidin-4-one (0.874g as prepared in Step 5). After two hours the resultant mixture was evaporated under reduced pressure. The residue was suspended in ether (9ml) and cooled. A suspension of 1-methyl cyclobutyl-1-amino chloride (0.320g as prepared in Step 7) and triethylamine (0.531g) in ether (6ml) was added. After twenty-four hours the resultant mixture was filtered and washed with ether. The filtrate was dried over magnesium sulphate and evaporated under reduced pressure. The

residue was chromatographed on silica, using hexane-ethylacetate to give the title compound (0.166g) as a yellow solid. [MPt 129.5-135.5°C].

NMR (CDCl3); δ 1.47(3h,s); 1.74-1.93(2h,m); 1.96-2.08(2H,m); 2.22-2.36(2H,m); 2.73(2H,m); 2.83(1H,m); 5.50(2H,s); 5.86(1H,bs); 7.45(1H,d); 7.53(1H,t); 7.76(1H,d); 7.84(1h,s).

The compounds listed below were prepared by analagous methods.

Compound 259: 5-[N-(1-methylcyclopentyl)-1-acetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one;
NMR (CDCl3); δ1.41(3H,s); 1.65(6H,m); 1.94(2H,m); 2.73(2H,m), 4.80(1H,m); 5.49(2H,s); 5.70(1H,bs); 7.47(1H,d); 7.54(1H,t), 7.76(1H,d), 7.83(1H,s).

Compound 261: 5-[N-(1-ethyl-1-cyclopropyl-1-acetamide]-3-(3-trifluoromethylphenyl)oxazolidin-4-one;
NMR(CDCl3): δ0-0.36(4h,m), 0.53-0.67(2H,m) 0.98(3H,t); 2.58(2H,m); 3.20(1H,q); 4.61(1H,m); 5.30(2H,s); 5.59(1H,bd); 7.25(1H,d); 7.32(1H,t); 7.56(1H,d); 7.63(1H,s).

Compound 263: 5-[N-(1-methylcyclohexyl)-1-acetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one;
NMR (CDCl3): δ 11.330-11.55(8H,m); 1.35(3H,s); 1.90-204(2H,m); 2.75(2H,m); 4.80(1H,m); 5.50(2H,s); 5.50(1H,bs); 7.46(1H,d); 7.53(1H,t); 7.76(1H,d); 7.84(1H,s).

Compound 264: 5-[N-(neopentyl)-1-acetamide]-3-(3-trifluoromethyl phenyl)oxazolidin-4-one;
NMR (CDCl3): δ 0.90(9H,s); 2.83(2H,m); 4.81(1H,m); 5.51(2H,s); 5.59(1H,bs); 7.46(1H,d); 7.53(1H,t); 7.77(1H,d); 7.82(1H,s).
Mpt: 117.5-122°C.

Compound 268: 5-[N-(1-methylcyclopropyl)-1-acetamido]-3-(3-trifluoromethylphenyl)oxazolidin-4-one;
NMR (CDCl3): δ 0.54(2H,m); 0.64(2H,m); 1.38(3H,s); 2.72(2H,m); 4.78(1H,m);

5.50(2H,s); 6.08(1H,bs); 7.45(1H,d); 7.53(1h,T); 7.77(1h,D); 7.85(1h,S). mpt: 182.5-184.5°c (dec).

EXAMPLE 97 **An alternative route to 3(3-hydrocarbyl-2,4-dioxoimidazolidin-1-yl)pyrrolidin-2-one (Compare Example 29) exemplified by Compound 334: 3(3-t-Butyl-2,4-dioxoimidazolidin-1-yl)-1(2,2-difluoro-1,3-benzodioxol-5-yl)pyrrolidin-2-one**

Sodium hydride (0.024g, 55% dispersion in mineral oil) was added to a stirred solution of 3-t-butyl-imidazolidine-2,4-dione (0.085g) in N,N-dimethylformamide (10ml) and the mixture allowed to stir for thirty minutes at room temperature. The stirred mixture was cooled to 0°C, treated with a solution of 1(2,2-difluoro-1,3-benzodioxol-5-yl)-3-iodopyrrolidinone(0.20g) in N,N-dimethylformamide (10ml), allowed to warm to room temperature, then to stir for a further two hours. It was then diluted with water and extracted with ethyl acetate. The extracts were washed with water and brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica, using dichloromethane-ethanol (49:1), then ethyl acetate-hexane (1:1), as eluants, to give the title compound (0.044g, m.p. 120-124°C). NMR ($CDCl_3$): δ 1.63(9H,s); 2.18(1H,m); 2.56(1H,m); 3.84(2H,q); 3.84(2H,m); 5.00(1H,dd); 7.06(1H,d); 7.13(1H,dd); 7.69(1H,d). MS: M^+ 395. Confirmation that the imidazolidine ring was not attached in an alternative manner was provided by ^{13}C NMR (pyrrolidinone methine carbon, 54.1ppm).

Intermediates and Analagous Methods of Preparation

EXAMPLE 98 **Preparation of 3-(2,2,2-Trifluoroethylamino)-1-(3-trifluoromethoxyphenyl-2-pyrrolidinone**

Step 1 Preparation of 3-iodo-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone

3-bromo-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone (prepared in a similar manner to that described in Step 1 of Example 10) (1.0g) was dissolved in acetone (20ml). To this solution was added sodium iodide (0.46g) and the reaction was stirred at room temperature for 4 hours under

a nitrogen atmosphere. A further 0.046g of sodium iodide was added and reaction left to stand for 12 hours. The precipitate was filtered off through a pad of Hyflo, washing with acetone. After evaporating the solvent the residue was dissolved in ethyl acetate, washed with brine (x2), dried ($MgSO_4$), filtered and concentrated to give the crude 3-iodopyrrolidinone (1.06g) which was used directly in Step 2.

Step 2 Preparation of 3-(2,2,2-Trifluoroethylamino)-1-(3-trifluoromethoxy)phenyl-2-pyrrolidine

3-Iodo-1-(3-trifluoromethoxy)phenyl-2-pyrrolidinone (prepared in Step 1) (1.06g) was mixed with 2,2,2-trifluoroethylamine (5.0g) at room temperature and then cooled to 0°C (ice/water bath cooling) and stirred for 17 hours. After standing at room temperature for 96 hours, the mixture was diluted with ethyl acetate, washed with water (x2), brine (x1), dried ($MgSO_4$), filtered and concentrated to give the crude amino pyrrolidinone title compound as an oil (0.924g).

EXAMPLE 99 **Preparation of 3(N-methylamino)-1-(3-trifluoromethylthio)-phenyl-2-pyrrolidinone**

Step 1 Preparation of 3-chloro-1-(3-trifluoromethylthio)-phenyl-2-pyrrolidinone

A solution of 3-hydroxy-1-(3-trifluoromethylthio)-phenyl-2-pyrrolidinone (prepared by a similar method to that described in Example 9) (1.0g) in thionyl chloride (5ml) was stirred at room temperature for two hours before heating to reflux for 16 hours. After cooling, the excess thionyl chloride was removed in vacuo and the residue purified by flash chromatography, eluting with 30% ethyl acetate/hexane to give the 3-chloropyrrolidinone as a pale yellow oil (0.81g).

Step 2

A solution of 3-chloro-1-(3-trifluoromethylthio)phenyl-2-pyrrolidinone (prepared as in Step 1) (0.80g) in THF (30ml) was treated

with a continuous stream of methylamine gas at room temperature for 1 hour. The reaction was then heated to reflux, maintaining the flow of methylamine. After 4 hours, the reaction was left to stand for 72 hours and then poured into saturated $NaHCO_3$ (aq) and extracted with ethyl acetate (x2). After drying ($MgSO_4$), the solvent was evaporated and the residue purified by chromatography, eluting with ethyl acetate then 30% methanol/ethyl acetate to give the amine title compound as a pale yellow oil which solidified (0.66g).

Compounds 199 and 201 may be prepared by methods similar to that described in Example 5 but using an intermediate I1 as starting material in place of the hydroxy compound. Compound 200 may be prepared by a method similar to that described in Example 27 but again using intermediate I1. The intermediate I1 is 3-(N-allyl)amino-1-3-bromophenyl-2-pyrrolidinone, a compound of general formula II in which A is 3-bromophenyl, X is CH_2 and R^{20} is $NH-CH_2-CH=CH_2$. For compounds 199 and 201 Compound I1 is reacted with the appropriate acyl chloride and for compound 200 it is reacted with t-butyl isocyanate.

Compound 202, 203 and 204 may all be prepared using methods similar to that described in Example 72 or Example 73. Compound I2, a compound of general formula III in which A is 3-(trifluoromethyl)phenyl, X is CH_2 and R^{20} is methane sulfonyloxy may be used as an intermediate for compound 204 and a similar intermediate may be used for Compounds 202 and 203.

Compounds 205 to 208 may be prepared by methods similar to those described in Examples 5, and 10 or 27 using as intermediates Compounds I3 (formula III, A is 3-chloro-4-fluorophenyl, X is CH_2 and R^{15} is methane sulfonyloxy), I4 (formula II, A is 3-chloro-4-fluorophenyl, X is CH_2 and R^{15} is NH_2) and I5 (formula II, A is 3-chloro-4-fluorophenyl, X is CH_2 and R^{15} is NHMe).

Compounds 209 and 210 may be prepared by methods similar to those described in Examples 27 and 5 respectively from intermediate I6 (formula II, (formula II, A is 3-chloro-4-fluorophenyl, X is CH_2 and R^{15} is $NH-CH_2-CH=CH_2$).

Compounds 211 and 212 may be prepared by methods similar to those described in Example 5 but starting from intermediates I4 and I5 respectively.

Compounds 213, 214 and 217 to 219, 221, 222, 224 to 231 and 233 may all be prepared by methods similar to those of Example 5. Compounds 220 and 232 may be prepared by methods similar to those of Example 20 and Compounds 215, 216 and 223 by methods similar to that of Example 10. Intermediates in the synthesis of these compounds include:

I7 (formula III, A is 3-(trifluoromethoxy)phenyl, X is CH_2 and R^{20} is methane sulfonyloxy);

I8 (formula II, A is 3-(trifluoromethoxy)phenyl, X is CH_2 and R^{15} is NH-CHO);

I9 (formula II, A is 3-(trifluoromethyl)phenyl, X is CH_2 and R^{15} is NH-CHO);

I10 (formula II, A is 3-(trifluoromethoxy)phenyl, X is CH_2 and R^{15} is NH-Me);

I11 (formula III, A is 3-bromophenyl, X is CH_2 and R^{20} is methane sulfonyloxy);

I12 (formula II, A is 3-bromophenyl, X is CH_2 and R^{15} is SH);

I13 (formula II, A is 3-bromophenyl, X is CH_2 and R^{15} is NMe); and

I14 (formula II, A is 3-bromophenyl, X is CH_2 and R^{15} is NH_2).

The pyrrolidinone compound 282 was prepared from 3-(methylamino)-1-[3- (trifluoromethoxy)phenyl]pyrrolidin-2-one (prepared in analogy to the procedure for the preparation of 3-(methylamino)-1-[3-(trifluoromethyl) phenyl]pyrrolidin-2-one described in Example 10 and trimethylsilylacetyl chloride and pyridine in dichloromethane.

Intermediates used in the preparation of Compounds 269, 271 and 271 include the compounds listed below.

2-(methylthio)-N-(3-trifluoromethoxyphenyl)acetamide

Prepared by a similar method to that described in Example 91, Step 1.
NMR($CDCl_3$) : δ 2.20(3H,s); 3.35(2H,s); 7.0(1H,d); 7.35(1H,t); 7.45(1H,d); 7.62(1H,s); 8.80(1H,bs).
MPt : 43.5-45°C.

N-(ethoxymethyl)-N-(3-trifluoromethoxyphenyl)-2-(methylthio)acetamide

Prepared by a similar method to that described in Example 91, Step 2.

NMR($CDCl_3$) : -dl 1.22(3H,t); 2.22(3H,s); 3.02(2H,bs); 3.68(2H,m); 5.10(2H,s); 7.18-7.29(3H,m); 7.47(1H,t).

N-(ethoxymethyl)-N-(3-trifluoromethoxy phenyl)-2-(methylsulphinyl)acetamide

Prepared by a similar method to that described in Example 91, Step 3.
NMR(CDCl3); δ 1.24(3H,t); 2.76(3H,s); 3.59(2H,d); 3.67(2H,q); 5.11(2H,d); 7.12(1H,s); 7.22-7.36(2H,m); 7.51(1H,t).

5-hydroxy-3-(3-trifluoromethoxy phenyl)oxazolidin-4-one

Prepared by a similar method to that described in Example 91, Step 4.
NMR($CDCl_3$) : δ 5.44(1H,s); 5.65(2H,s); 7.06-7.16(1H,m);7.37-7.45(2H,m); 7.60(1H,s|).

5-[methylamino]-3-(3-trifluoromethoxy phenyl)oxazolidin-4-one

Prepared by a similar method to that described in Example 91, Step 6 (used for Compound 269);
NMR($CDCl_3$) : δ 22.57(3H,s); 5.18(1H,s); 5.41(1H,m); 5.47(1H,m); 7.05-7.13(1H,m); 7.13-7.33(2H,m); 7.61(1H,s).

5-amino-3-(3-trifluoromethoxy phenyl)oxazolidin-4-one

Prepared by a similar method to that described in Example 91, Step 6 (used for Compound 271);
NMR($CDCl_3$) : δ 1.62(2H,bs); 5.20(1H,bs); 5.37(1H,d); 5.45(1H,d); 7.03-7.13(1H,m); 7.32-7.47(2H,m); 7.60(1H,s).

5-(N-ethylamino)-3-(3-trifluoromethoxyphenyl)oxazolidin-4-one

Prepared by a similar method to that described in Example 91, Step 6 (used for Compound 270);
NMR($CDCl_3$) : δ 1.25(3H,t); 2.90(2H,q); 4.27(1H,bs); 5.20(1H,s); 5.40(1H,m); 5.46(1H,m); 7.04-7.11(1H,m); 7.38-7.50(2H,m); 7.60(1H,s).

Intermediates in the preparation of Compounds 259, 261, 263, 264 and 268 are detailed below.

5-methylenechlorocarbonyl)-3-(3-trifluoromethylphenyl)oxazolidine

Prepared by a method similar to that described in Example 96, Step 8.

NMR(CDCl3): δ 3.52(2h,m); 4.79(1H,m); 5.52(2H,s); 7.50(1H,d); 7.55(1H,t); 7.75(1H,d); 7.80(1H,s).

1-methylcyclopentyl-1-acetamide

Prepared by a method similar to that described in Example 96, Step 6.
NMR (CDCls) : δ 11.40(3H,s); 1.56-1.78(8H,m); 1.93(3H,s); 5.39(1H,bs).

1-methylcyclopentyl-1-amine

Prepared by a method similar to that described in Example 96, Step 7 (used for the preparation of Compound 259)
NMR(CDCl3) : δ 1.27(3H,s); 1.40-1.82(10H,bm).

1-ethyl-1-cyclopropyl acetamide

Prepared by a method similar to that described in Example 96, Step 6 (used for the preparation of Compound 261)
NMR(CDCl3) : δ 0-0.34(4H,m); 0.60-0.75(1H,m); 0.97(3H,d); 1.74(3H,s); 2.03-2.13(1H,m).

1-ethyl-1-cyclopropyl aminochloride

Prepared by a method similar to that described in Example 96, Step 7 (used in the preparation of Compound 261).
NMR(CDCl3) : δ 0-0.6(1H,m); 0.12-0.30(3H,m); 0.51-0.72(1H,m); 0.97(3H,d); 2.13-2.21(1H,m); 7.84(3H,bs).
MPt: 130-155°C.

1-methylcyclohexyl-1-acetamide

Prepared by a method similar to that described in Example 96, Step 6 (used in the preparation of Compound 263).
NMR(CDCl3) : δ 1.37(3H,s); 1.23-1.55(8H,m); 1.92-2.02(2H,m); 1.95(3H,s); 5.18(1H,bs).
MPt : 83.5-86°C.

1-methylcyclohexyl-1-aminochloride

Prepared by a method similar to that described in Example 96, Step 7 (used in the preparation of Compound 263).
NMR(CDCl3) : δ 1.16(3H,s); 1.23-1.44(4H,m); 1.44-1.60(6H,m); 7.57(3H,bs).

(1-methylcyclopropyl)-1-t-butoxy carbamate (used in the preparation of 1-methylcyclopropyl)-1-aminochloride).

Diphenylphosphonyl azide (14.83g) was added in one go to a solution of 1-methylcyclo propane carboxzylic acid (5.00g) in tert-butanol (150ml). After twenty minutes triethylamine (8.4ml) was added to the resultant mixture which was then heated under reflux under N_2 for five hours. The resultant mixture was quenched with water and extracted with ther. The extracts were washed with water and brine dried over magnesium sulphate and evaporated under reduced pressure. Ether was added to the residue by filtration. The filtrate was dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (4.85g) as a white solid.

NMR(CDCl3) : δ 0.52-0.60(2H,m); 0.70-0.76(2H,m); 1.33(3H,s); 1.44(9H,s).

MPt : 69.5-77°C.

1-methyl cyclopropyl-1-amino chloride
(Used in the preparation of Compound 268).

Hydrogen chloride was bubbled through a solution of (1-methyl cyclopropyl)-1-t-butoxy carbamate (4.49g prepared as described) in ethanol. The resultant mixture weas evaporated under reduced pressure. Ether was added to the residue, this was then filtered to give the title compound (1.56g) as a white solid.
NMR(CDCl3): δ 0.60(2H,t); 0.90(2H,t); 1.34(3h,s); 8.43(3H,bs)
MPt : 193-206°C (dec).

Structural details and characterising data for the intermediates I59 and I60 are given in Tables II and III. These intermediates are used in the synthesis of Compound 329.

The intermediate I61 is a compound of general formula VI in which A is 2-trifluoromethylbenzoxazol-6-yl. It is used in the preparation of Compound 332. Other intermediates in the synthesis of Compound 332 include intermediates I62 and I63, details of which are given in Tables II and III.

Intermediates I64 and I65 are used in the preparation of Compound 331. Further details of these intermediates are given in Tables II and III.

The intermediate I66 is used in the preparation of Compound 339. I66 is a compound of general formula XXVII in which A is 2,2-bis(difluoromethoxy)pyrimidin-4-yl, R^2, R^3, R^4 and R^5 are all hydrogen, R^1 is t-butyl and R^{25} is I. This compound is prepared from the intermediate 4-amino-2,6-bis(difluoromethoxy)pyrimidine (m.p. 102-103°C) which, in turn, is prepared by treating 4-amino-2,6-dihydroxypyrimidine with chlorofluoromethane in aqueous dioxane in the present of sodium hydroxide in a manner similar to that described in Example 66, for the intermediate to Compound 181.

NMR ($CDCl_3$): δ 1.35(9H,s); 2.4(2H,m); 3.25(2H,t); 5.05(1H,bs); 5.25(1H,dd); 7.25(1H,t); 7.35(1H,t); 7.5(1H,s); 9.0(1H,bs). MS: MH^+ 539.

The intermediate I67 is used in the preparation of Compound 332. I67 is a compound of general formula XXVII in which A is 5-methoxycarbonyl-thiazol-2-yl, R^2, R^3, R^4 and R^5 are all hydrogen, R^1 is t-butyl and R^{25} is I.

NMR and melting point details are given in Table III.

The intermediate I68 is used in the preparation of Compound 333. I68 is a compound of general formula XXVII in which A is 5-thiocyanato-thiazol-2-yl, R^2, R^3, R^4 and R^5 are all hydrogen, R^1 is t-butyl and R^{25} is I. NMR and melting point details are given in Table III.

Intermediate I69 is used in the preparation of Compounds 273-277. Intermediates I70, I72 and I73 are used in the preparation of Compounds 283-290; 291-292; and 295-296 respectively.

Structural details for intermediates are given in Table II and characterising data for Compounds 199 to 233 and intermediates I1 to I68 are given in Table III. All of the compounds of Table II are of either general formula II, III or IV.

TABLE II

Int No.	Prep.	A	X	R15/R20
I1		m-OBr Ph	CH2	NHCH2CH=CH2
I2		m-CF3 Ph Ph	CH2	OSO2Me
I3		m-Cl Ph, p-F Ph	CH2	OSO2Me
I4		m-Cl Ph, p-F Ph	CH2	NH2
I5		m-Cl Ph, p-F Ph	CH2	NHMe
I6		m-Cl Ph, p-F Ph	CH2	NHCH2CH=CH2
I7		OCF3 Ph	CH2	OSO2Me
I8		OCF3 Ph	CH2	NHCHO
I9		CF3 Ph	CH2	NHCHO
I10		OCF3 Ph	CH2	NHMe
I11		m-Br Ph	CH2	OSO2Me
I12		m-Br Ph	CH2	SH
I13		m-Br Ph	CH2	NHMe
I14		m-Br Ph	CH2	NH2
I15	ex 99, step 1	m-SCF3 Ph	CH2	Cl
I16	ex 10, step 1	m-CF3 Ph	CH2	Br
I17	ex 10, step 1b	m-OCF3 Ph	CH2	Br
I18	ex 10, step 1	m-OCHF2 Ph	CH2	Br
I19	ex 10, step 1	m-Cl Ph	CH2	Br
I20	ex 98, step 1	m-OCF3 Ph	CH2	I
I21	ex 9, step 1a	m-OCF3 Ph	CH2	OH
I22	ex 9, step 1	m-OCHF2 Ph	CH2	OH
I23	ex 9, step 1a	m-SCF3 Ph	CH2	OH
I24	ex 1, step 3	m-CF3 Ph	CH2	N3
I25	ex 1, step 3	m-OCF3 Ph	CH2	N3
I26	ex 1, step 3	m-OCHF2 Ph	CH2	N3
I27	ex 1, step 4	m-CF3 Ph	CH2	NH2

Int No.	Prep.	A	X	R15/R20
I28	ex 1, step 4	m-OCF3 Ph	CH2	NH2
I29	ex 1, step 4	m-OCHF2 Ph	CH2	NH2
I30	ex 10, step 2	m-CF3 Ph	CH2	NHMe
I31	ex 10, step 2	m-OCF3 Ph	CH2	NHMe
I32	ex 10, step 2	m-OCHF2 Ph	CH2	NHMe
I33	ex 99, step 2	m-SCF3 Ph	CH2	NHMe
I34	ex 27, step 1	m-OCF3 Ph	CH2	NHEt
I35	ex 27, step 1	m-OCHF2 Ph	CH2	NHEt
I36	ex 27, step 1	m-OCF3 Ph	CH2	NHPr
I37	ex 27, step 1	m-CF3 Ph	CH2	NHCH(CH3)2
I38	ex 27, step 1	m-CF3 Ph	CH2	NHCH2CH2OMe
I39	ex 27, step 1	m-OCF3 Ph	CH2	NHCH2CH2SMe
I40	ex 27, step 1	m-CF3 Ph	CH2	NH-cyclopropyl
I41	ex 27, step 1	m-OCF3 Ph	CH2	NHCH2CH2N(Me)2
I42	ex 27, step 1	m-OCF3 Ph	CH2	NHCH2CH2OH
I43	ex 27, step 1	m-OCF3 Ph	CH2	NHCH2CCH
I44	ex 27, step 1	m-CF3 Ph	CH2	NCH2CH=CH2
I45	ex 27, step 1	m-OCF3 Ph	CH2	NCH2CH=CH2
I46	ex 27, step 1	m-OCF3 Ph	CH2	NHCH2CH(OMe)2
I47	ex 27, step 1	m-CF3 Ph	CH2	NHCH2Ph
I48	ex 27, step 1	m-CF3 Ph	CH2	NHPh
I49	ex 98, step 2	m-OCF3 Ph	CH2	NHCH2CF3
I50	ex 24, step 1	m-CF3 Ph	CH2	NHOMe

Int No.	Prep.	A	X	R15/R20
I51	ex 23, step 1	m-CF3 Ph	CH2	NHCH2CO2Et
I52	ex 23, step 1	m-OCF3 Ph	CH2	NHCHCO2Me
I53	ex 23, step 1	m-OCF3 Ph	CH2	NHCH2CO2C(CH3)3
I54	ex 23, step 1	m-OCF3 Ph	CH2	NHCH2COC(CH3)3
I55	ex 23, step 1	m-OCF3 Ph	CH2	NHCH2CN
I56	ex 20, step 1	m-CF3 Ph	CH2	SAc
I57	ex 20, step 1	m-OCF3 Ph	CH2	SAc
I58	ex 20, step 1	m-OCHF2 Ph	CH2	SAc
I59		2-trifluoromethyl benzoxazol-5-yl	S	H
I60		2-trifluoromethyl benzoxazol-5-yl	S	OH
I62		2-trifluoromethyl benzoxazol-6-yl	S	H
I63		2-trifluoromethyl benzoxazol-6-yl	S	OH
I64		1,3-benzodioxol-5 yl	S	H
I65		1,3-benzodioxol-5 yl	S	OH
I69		m-OCHF2 Ph	O	CH2CO2H
I70		m-CF3 Ph	S	NHCH2CH2CH3
I72		m-CF3 Ph	S	NHEt
I73		m-CF3 Ph	S	NH-CH2CH=CH2

TABLE III

No.	Prep	mpt	nmr
16	ex 8	128-129	1.63 (6H, d), 1.90-2.08 (1H, m), 2.32 (1H, s), 2.42 (1H, dd), 2.40-2.59 (1H, m), 2.65 (1H, dd), 3.0-3.12 (1H, m), 3.76-3.93 (2H, m), 6.54 (1H, br s), 7.51 (1H, d), 7.60 (1H, t), 7.85 (1H, d), 7.89 (1H, br s)
17	ex 16	117	0.84 (3H, t), 1.29 (6H, s), 1.71 (2H, q), 1.90-2.08 (1H, m), 2.39 (1H, dd), 2.44-2.57 (1H, m), 2.72 (1H, dd), 2.95-3.08 (1H, m), 3.76-3.90 (3H, m), 5.86 (1H, br s), 7.40 (1H, d), 7.50 (1H, t), 7.85-7.81 (2H, m)
18	ex 16	111	1.42 (6H, s), 1.90-2.08 (1H, m), 2.40 (1H, dd), 2.44-2.57 (1H, m), 2.74 (1H, dd), 2.99-3.12 (1H, m), 3.75-3.91 (2H, m), 5.02 (1H, d), 5.10 (1H, d), 6.01 (1H, dd), 6.15 (1H, br s), 7.40 (1H, br d), 7.50 (1H, t), 7.82-7.91 (2H, m)
19	ex 27	112-114	1.28 (3H, t), 1.38 (9H, s), 2.25-2.53 (2H, m), 3.11-3.38 (2H, m), 3.71-3.95 (2H, m), 4.41 (1H, br s), 4.65 (1H, dd), 7.37 (1H, d), 7.47 (1H, t), 7.87-7.95 (2H, m)
20	ex 10	146-147	1.67 (6H, 2s), 2.08-2.25 (1H, m), 2.43-2.56 (1H, m), 2.88 (3H, s), 3.74-3.90 (2H, m), 4.73 (1H, br s), 5.22 (1H, dd), 7.41 (1H, br d), 7.49 (1H, t), 7.86-7.95 (2H, m)
22	ex 8	137-138	1.95-2.11 (1H, m), 2.50-2.70 (2H, m), 2.96 (1H, dd), 3.10-3.25 (1H, m), 3.79-3.98 (2H, m), 7.09 (1H, t), 7.30 (2H, t), 7.40-7.56 (4H, m), 7.82-7.93 (2H, m), 8.70 (1H, br s)
23	ex 8	110	1.15 (3H, t), 1.90-2.08 (1H, m), 2.39-2.58 (2H, m), 2.78 (1H, dd), 3.0-3.15 (1H, m), 3.25-3.38 (2H, m), 3.76-3.95 (2H, m), 6.24 (1H, br s), 7.42 (1H, br d), 7.50 (1H, br t), 7.86 (1H, br d), 7.92 (1H, br s)
24	ex 18	146-147	1.60-2.05 (5H, m), 2.25-2.58 (3H, m), 2.74 (1H, dd); 2.97-3.12 (1H, m), 3.75-3.82 (2H, m), 4.28 4.43 (1H, m), 6.40 (1H, br m), 7.41 (1H, d), 7.50 (1H, t), 7.85 (1H, br d), 7.90 (1H, br s)

No.	Prep	mpt	nmr
25	ex 18	96.5-99	1.25 (3H, t), 1.53 (6H, 2s), 1.90-2.10 (1H, m), 2.45 (1H, dd), 2.42-2.56 (1H, m), 2.78 (1H, dd), 3.00-3.14 (1H, m), 3.76-3.91 (2H, m), 4.18 (2H, q), 6.75 (1H, br s), 7.40 (1H, br d), 7.49 (1H, t), 7.85 (1H, d), 7.90 (1H, br s)
26	ex 12	128-131	1.90-2.08 (1H, m), 2.50-2.66 (2H, m), 3.06 (1H, dd), 3.12-3.27 (1H, m), 3.79-3.95 (2H, m), 6.90 (1H, d), 7.40 (1H, d), 7.49 (1H, t), 7.58 (1H, t), 7.86-7.98 (2H, m), 8.31 (1H, br s)
27	ex 12	oil	1.87-2.03 (1H, m), 2.49 (1H, t), 2.49-2.62 (1H, m), 2.63 (1H, dd), 3.04 (1H, dd), 3.05-3.18 (1H, m), 3.80-3.94 (2H, m), 4.74 (2H, d), 7.40 (1H, d), 7.48 (1H, t), 7.85-7.90 (2H, m)
28	ex 1	175-176	1.31 (9H, s), 1.96-2.15 (1H, m), 2.75-2.90 (1H, m), 3.75-3.90 (2H, m), 4.40-4.55 (1H, m), 5.20 (1H, br s), 5.50 (1H, br d), 7.41 (1H, d), 7.47 (1H, t), 7.79 (1H, d), 7.92 (1H, br s)
29	ex 5	138-139	1.08 (9H, s), 1.90-2.08 (1H, m), 2.16 (2H, s), 2.85-2.97 (1H, m), 3.79-3.93 (2H, m), 4.52-4.64 (1H, m), 6.18 (1H, br d), 7.42 (1H, d), 7.50 (1H, t), 7.85 (1H, d), 7.93 (1H, br s)
30	ex 12	oil	1.38 (9H, s), 1.87-2.06 (1H, m), 2.46-2.60 (1H, m), 2.91 (1H, dt), 3.10-3.35 (2H, m), 3.80-3.95 (2H, m), 7.40 (1H, d), 7.49 (1H, t), 7.82-7.92 (2H, m)
31	ex 8	87-90	0.95-1.02 (6H, m), 1.72-1.90 (2H, m), 1.90-2.20 (3H, m), 2.45 (1H, dd), 2.43-2.56 (1H, m), 2.76 (1H, dd), 3.00-3.11 (1H, m), 3.76-3.91 (2H, m), 6.24 (1H, br s), 7.40 (1H, d), 7.49 (1H, t), 7.82-7.91 (2H, m)
32	ex 19	107.5-111	1.15 (3H, d), 1.37 (9H, s), 2.02-2.10 (1H, m), 2.26-2.38 (1H, m), 2.66-2.77 (1H, m), 2.99-3.09 (1H, m), 3.75-3.84 (2H, m), 5.66 (1H, br s), 7.38 (1H, br d), 7.48 (1H, t), 7.83-7.90 (2H, m)
33	ex 12	oil	0.77 (6H, t), 1.20 (3H, s), 1.48-1.80 (6H, m), 1.90-2.05 (1H, m), 2.50-2.70 (1H, m), 3.80-3.95 (3H, m), 5.50 (1H, s), 7.36-7.55 (2H, m), 7.81-7.95 (2H, m)

No.	Prep	mpt	nmr
34	ex 16	104-105	0.89 (3H, t), 1.32 (6H, s), 1.74 (2H, q), 2.07-2.23 (1H, m), 2.42-2.55 (1H, m), 2.87 (3H, s), 3.73-3.90 (2H, m), 4.40 (1H, br s), 5.22 (1H, dd), 7.40 (1H, br d), 7.49 (1H, t), 7.88 (1H, br d), 7.96 (1H, br s)
35	ex 16	120-121	1.46 (6H, s), 2.05-2.24 (1H, m), 2.42-2.55 (1H, m), 2.89 (3H, s), 3.73-3.90 (2H, m), 4.63 (1H, br s), 5.04 (1H, d), 5.12 (1H, d), 5.21 (1H, dd), 6.07 (1H, dd), 7.40 (1H, d), 7.49 (1H, t), 7.88 (1H, br d), 7.95 (1H, br s)
36	ex 10	132-133	1.37 (9H, s), 2.04-2.21 (1H, m), 2.41-2.55 (1H, m), 2.85 (3H, s), 3.70-3.86 (2H, m), 4.45 (1H, br s), 5.22 (1H, dd), 6.99-7.04 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.70 (1H, br s)
37	ex 10	167-169	2.17-2.34 (1H, m), 2.45-2.58 (1H, m), 3.07 (3H, s), 3.75-3.93 (2H, m), 5.08 (1H, dd), 7.01 (1H, t), 7.12 (1H, s), 7.22-7.31 (2H, m), 7.42 (3H, dd), 7.50 (1H, t), 7.87 (1H, br d), 7.96 (1H br s)
38	ex 27	157-158	1.24 (3H, d), 1.31 (3H, d), 1.33 (9H, s), 2.22-2.37 (1H, m), 2.51-2.69 (1H, m), 3.70-3.84 (2H, m), 3.89-4.00 (2H, m), 4.30 (1H, br s), 7.35 (1H, br d), 7.45 (1H, t), 7.90 (1H, br d), 7.95 (1H, br s)
41	ex 20	104-106	1.38 (9H, s), 2.16-2.32 (1H, m), 2.69-2.72 (1H, m), 3.81-3.92 (2H, m), 4.35 (1H, t), 5.63 (1H, br s), 7.00-7.07 (1H, m), 7.39 (1H, t), 7.55 (1H, dd), 7.64 (1H, br s)
42	ex 20	119-120	1.38 (9H, s), 2.18-2.34 (1H, m), 2.71-2.85 (1H, m), 3.85-3.95 (1H, m), 4.35 (1H, t), 5.62 (1H, br s), 7.42 (1H, d), 7.50 (1H, t), 7.85-7.94 (2H, m)
43	ex 10	127-128	1.66 (6H, 2s), 2.06-2.34 (1H, m), 2.34 (1H, s), 2.43-2.56 (1H, m), 2.88 (2H, m), 4.72 (1H, br s), 5.22 (1H, dd), 7.40 (2H, m), 7.84-7.93 (2H, m)

No.	Prep	mpt	nmr
44	ex 10	136-137	1.37 (9H, s), 2.05-2.21 (1H, m), 2.41-2.55(1H, m), 2.85 (3H, s), 3.71-3.88 (2H, m), 4.45 (1H, br s), 5.21 (1H, dd), 7.38-7.46 (2H, m), 7.84-7.94 (2H, m)
51	ex 5	66.5-68.5	10:1 Rotamer mixture : 1.10 (9H, s), 2.10-2.53 (4H, m), 2.88 and 3.08 (3H, 2s), 3.72-3.93 (2H, m), 4.88 and 5.23 (1H, 2t), 6.99-7.10 (1H, m), 7.38 (1H, t), 7.54-7.70 (2H, m)
52	ex 10	135.5-136.5	1.66 (6H, d), 2.06-2.23 (1H, m), 2.34 (1H, s), 2.42-2.56 (1H, m), 2.87 (3H, s), 3.70-3.88 (2H, m), 4.72 (1H, br s), 5.22 (1H, dd), 6.97-7.05 (1H, m), 7.39 (1H, t), 7.55 (1H, dd), 7.68 (1H, br s)
53	ex 1	175-176.5	1.33 (9H, s), 1.91-2.08 (1H, m), 2.78-2.90 (1H, m), 3.80 (2H, dd), 4.40-4.50 (1H, m), 4.86 (1H, br s), 5.20 (1H, br d), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.48-7.53 (1H, m), 7.66 (1H br s)
54	ex 5	135-136	1.06 (9H, s), 1.87-2.05 (1H, m), 2.15 (2H, s), 2.84-2.97 (1H, m), 3.82 (1H, dd), 4.50-4.61 (1H, m), 6.12 (1H, br d), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.49-7.55 (1H, m), 7.69 (1H, br s)
55	ex 1	155-157	1.62 (6H, 2s), 1.95-2.13 (1H, m), 2.44 (1H, s), 2.81-2.94 (1H, m), 3.75-3.85 (2H, m), 4.45-4.57 (1H, m), 5.31 (1H, br s), 5.99 (1H, br d), 7.00 7.06 (1H, m), 7.39 (1H, t), 7.50 (1H, dd), 7.68 (1H, br s)
56	ex 16	98-99	0.87 (3H, t), 1.31 (6H, s), 1.73 (2H, q), 2.04-2.21 (1H, m), 2.40-2.53 (1H, m), 2.85 (3H, s), 3.68-3.87 (2H, m), 4.36 (1H, br s), 5.21 (1H, dd), 6.97-7.05 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.69 (1H, br s)
57	ex 16	171-172	0.87 (3H, t), 1.29 (6H, d), 1.69 (2H, q), 1.91-2.10 (1H, m), 2.78-2.90 (1H, m), 3.80 (2H, dd), 4.38-4.48 (1H, m), 4.75 (1H, br s), 5.19 (1H, br d), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.52 (1H, dd), 7.67 (1H, br s)

No.	Prep	mpt	nmr
58	ex 21	106-107	3:2 Rotamer mixture : 1.43 and 1.49 (9H, 2s), 2.11-2.35 (1H, m), 2.35-2.54 (1H, m), 2.89 and 2.96 (3H, 2s), 3.69-3.89 (2H, m), 4.53 and 4.99 (1H, 2 br t), 7.02 (1H d), 7.39 (1H, t), 7.58 (1H, d), 7.68 (1H, br s)
59	ex 21	136-137	1.47 (9H, s), 1.94-2.12 (1H, m), 2.73-2.90 (1H, m), 3.75-3.85 (2H, m), 4.30-4.44 (1H, m), 5.14-5.30 (1H, v br s), 7.00-7.08 (1H, m), 7.40 (1H, t), 7.55 (1H, dd), 7.65 (1H, br s)
60	ex 10	134-135	1.36 (9H, s), 2.10 (1H, m), 2.46 (1H, m), 2.83 (3H, s), 3.77 (2H, m), 4.43 (1H, br s), 5.21 (1H, dd), 7.12 (1H, m), 7.29 (1H, t), 7.57 (1H, t), 7.72 (1H, m)
61	ex 21	135-136	5:4 Rotamer mixture : 1.44 and 1.50 (9H, 2s), 2.14-2.37 (1H, m), 2.40-2.55 (1H, m), 2.89 and 2.96 (3H, 2s), 3.82-3.90 (2H, m), 4.55 and 4.98 (1H, 2t), 7.41 (1H, d), 7.50 (1H, br t), 7.82-8.00 (2H, m)
63	ex 5	gum	10:1 Rotamer mixture : 1.11 (9H, s), 2.12-2.30 (1H, m), 2.29 (1H, d), 2.38 (1H, d), 2.40-2.55 (1H, m), 3.08 (3H, s), 3.76-3.96 (2H, m), 5.20 (1H, dd), 7.40 (1H, d), 7.58 (1H, t), 7.86-7.94 (2H, m)
64	ex 27	108.5-110	1.28 (1H, t), 1.36 (9H, s), 2.22-2.50 (2H, m), 3.11-3.37 (2H, m), 3.67-3.90 (2H, m), 4.41 (1H, br s), 4.68 (1H, dd), 6.96-7.04 (1H, m), 7.36 (1H, t), 7.58 (1H, dd), 7.69 (1H, br s)
65	ex 27	146-148	1.30 (3H, t), 1.66 (6H, d), 2.30-2.54 (2H, m), 2.33 (1H, s), 3.15-3.37 (2H, m), 3.68-3.91 (2H, m), 4.60-4.71 (2H, m), 6.97-7.03 (1H, m), 7.36 (1H, t), 7.56 (1H, dd), 7,68 (1H, br s)
69	ex 21	147-148	1.46 (9H, s), 1.95-2.15 (1H, m), 2.72-2.88 (1H, br m), 3.79-3.87 (2H, m), 4.30-4.45 (1H, br m), 5.21 (1H, br s), 7.42 (1H, d), 7.50 (1H, t), 7.85-7.94 (2H, m)

No.	Prep	mpt	nmr
70	ex 10	133-135	1.36 (9H, s), 2.02-2.20 (1H, m), 2.41-2.54 (1H, m), 2.84 (3H, s), 3.70-3.86 (2H, m), 4.44 (1H, br s), 5.18-5.27 (1H, dd), 6.54 (1H, t), 6.92 (1H, dd), 7.35 (1H, t), 7.45 (1H, dd), 7.60 (1H, t)
71	ex 10	122-123	1.67 (6H, 2s), 2.05-2.22 (1H, m), 2.42-2.55 (1H, m), 2.87 (3H, s), 3.70-3.86 (2H, m), 4.73 (1H, br s), 5.24 (1H, dd), 6.54 (1H, t), 6.92 (1H, dd), 7.35 (1H, t), 7.45 (1H, dd), 7.60 (1H, t)
72	ex 5	gum	1.08 (9H, s), 2.08-2.28 (1H, m), 2.09 (1H, d), 2.36 (1H, d), 2.36-2.52 (1H, m), 3.06 (3H, s), 3.72-3.92 (2H, m), 5.23 (1H, dd), 6.53 (1H, t), 6.92 (1H, dd), 7.35 (1H, t), 7.45 (1H, dd), 7.59 (1H, t)
73	ex 21	139-140	5:4 Rotamer mixture : 1.44 and 1.48 (9H, 2s), 2.12-2.35 (1H, m), 2.38-2.53 (1H, m), 2.88 and 2.96 (3H, 2s), 3.69-3.87 (2H, m), 4.51 and 4.99 (1H, 2 br t), 6.54 (1H, t), 6.92 (1H, br d), 7.35 (1H, t), 7.41-7.52 (1H, br m), 7.60 (br s)
74	ex 16	77-81	1.26 (3H, t), 1.33 (6H, s), 1.67-1.78 (2H, m), 2.01-2.20 (1H, m), 2.40-2.52 (1H, m), 2.85 (3H, s), 3.69-3.85 (2H, m), 4.36 (1H, br s), 5.21 (1H, dd), 6.53 (1H, t), 6.91 (1H, dd), 7.35 (1H, t), 7.45 (1H, dd), 7.61 (1H, t)
75	ex 20	111-112.5	1.66 (9H, s), 2.20-2.35 (1H, m), 2.39 (1H, s), 2.72-2.86 (1H, m), 3.86-3.95 (2H, m), 4.40 (1H, t), 6.07 (1H, br s), 7.39-7.54 (2H, m), 7.84-7.92 (2H, m)
76	ex 20	83-86	1.66 (6H, s), 2.18-2.32 (1H, m), 2.40 (1H, s), 2.70-2.85 (1H, m), 3.81-3.92 (2H, m), 4.39 (1H, t), 6.09 (1H, br s), 7.00-7.08 (1H, m), 7.40 (1H, t), 7.50-7.58 (1H, m), 7.62-7.66 (1H, m)
77	ex 22	80-92	1.52 (9H, s), 2.16-2.33 (1H, m), 2.64-2.76 (1H, m), 3.75-3.93 (2H, m), 5.36 (1H, t), 7.05 (1H, dt), 7.40 (1H, t), 7.58 (1H, dd), 7.65 (1H, br s)

No.	Prep	mpt	nmr
78	ex 27	110-111.5	0.96 (3H, t), 1.35 (9H, s), 1.55-1.81 (2H, m), 2.30-2.50 (2H, m), 3.02-3.22 (2H, m), 3.68-3.78 (1H, m), 3.81-3.91 (1H, m), 4.40 (1H, br s), 4.53 (1H, dd), 6.95-7.03 (1H, m), 7.36 (1H, t), 7.58 (1H, dd), 7.68 (1H, br s)
79	ex 16	gum	0.90 (3H, t), 1.33 (6H, s), 1.72 (2H, q), 2.18-2.35 (1H, m), 2.70-2.85 (1H, m), 3.85-3.94 (2H, m), 4.35 (1H, t), 5.50 (1H, br s), 7.42 (1H, d), 7.50 (1H, t), 7.85-7.92 (2H, m)
80	ex 16	83-84.5	0.90 (3H, t), 1.32 (6H, s), 1.72 (2H, q), 2.15-2.34 (1H, m), 2.68-2.84 (1H, m), 3.82-3.90 (2H, m), 4.35 (1H, t), 5.52 (1H, br s), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.52-7.59 (1H, m), 7.65 (1H, br s)
81	ex 22	105-108	1.53 (9H, s), 2.34-2.51 (2H, m), 3.78-3.88 (2H, m), 3.82 (3H, s), 4.96 (1H, t), 7.41 (1H, br d), 7.50 (1H, t), 7.90 (1H, br s), 7.95 (1H, br d)
82	ex 27	136.5-138.5	1.31 (9H, s), 2.35-2.50 (1H, m), 2.54-2.71 (1H, m), 3.16-3.29 (1H, m), 3.66-4.00 (4H, m), 4.24 (1H, t), 4.63 (1H, br t), 5.06 (1H, br s), 6.99 7.06 (1H, m), 7.37 (1H, t), 7.53-7.63 (2H, m)
83	ex 27	gum	1.25 (9H, s), 2.27-2.50 (2H, m), 2.67-2.83 (2H, m), 4.15 (1H, br s), 5.04 (1H t), 7.31-7.50 (7H, m), 7.86 (1H, d), 7.95 (1H, br s)
84	ex 27	111-112	1.34 (9H, s), 2.14-2.30 (1H, m), 2.44-2.57 (1H, m), 3.32-3.40 (2H, m), 3.44 (3H, s), 3.70-3.91 (3H, m), 4.86 (1H, dd), 6.34 (1H, br s), 7.38 (1H, br d), 7.47 (1H, t), 7.86-7.95 (2H, m)
85	ex 27	137-138	0.79-0.91 (4H, m), 1.35 (9H, s), 2.29-2.41 (1H, m), 2.48-2.66 (1H, m), 2.65-2.76 (1H, m), 3.75 (1H, q), 3.87-3.98 (1H, m), 5.31 (1H, br s), 7.35 (1H, d), 7.45 (1H, t), 7.90 (1H, d), 7.95 (1H, br s)
86	ex 24	127.5-128.5	1.41 (9H, s), 2.26-2.39 (1H, m), 2.39-2.55 (1H, m), 3.74-3.90 (2H, m), 3.78 (3H, s), 5.12 (1H, dd), 5.90 (1H, br s), 7.40 (1H, d), 7.48 (1H, t), 7.87-7.97 (2H, m)

No.	Prep	mpt	nmr
87	ex 27	115-116	1.10 (9H, s), 2.12-2.28 (1H, m), 2.33-2.48 (1H, m), 3.58--3.78 (2H, m), 4.24-4.49 (3H, m), 4.85 4.97 (1H, m), 7.17-7.41 (7H, m), 7.75 (1H, br d), 7.91 (1H, s)
88	ex 24	102-104	1.41 (9H, s), 2.24-2.37 (1H, m), 2.39-2.51 (1H, m), 3.68-3.87 (2H, m), 3.77 (3H, s), 5.11 (1H, dd), 5.89 (1H, br s), 6.52 (1H, t), 6.92 (1H, dd), 7.34 (1H, t), 7.47 (1H, dt), 7.58 (1H, t)
89	ex 5	72-73	1.10 (9H, s), 2.40 (2H, s), 2.41-2.53 (2H, m), 3.78-3.88 (1H, m), 3.85 (3H, s), 3.90-4.00 (1H, m), 5.04 (1H, t), 7.41 (1H, br d), 7.49 (1H, t), 7.89-7.95 (2H, m)
90	ex 27	95-96.5	1.33 (9H, s), 2.11-2.29 (1H, m), 2.45-2.59 (1H, m), 3.16-3.37 (2H, m), 3.49 (3H, s), 3.53 (3H, s), 3.69-3.90 (2H, m), 4.68 (1H, t), 4.85 (1H, dd), 6.25 (1H, br s), 6.97-7.05 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.68 (1H, br s)
91	ex 27	136.5-137.5	2.23-2.41 (1H, m), 2.38 (1H, t), 2.48-2.60 (1H, m), 3.70-3.90 (2H, m), 3.93 (1H, dd), 4.05 (1H, dd), 4.92 (1H, br s), 5.07 (1H, dd), 7.00-7.07 (1H, m), 7.39 (1H, t), 7.57 (1H, dd), 7.67 (1H, br s)
92	ex 27	solid gum	1.36 (9H, s), 2.20-2.38 (1H, m), 2.40-2.59 (1H, m), 2.68 (6H, s), 3.10-3.22 (2H, m), 3.56-3.68 (2H, m), 3.68-3.83 (1H, m), 3.83-3.96 (1H, m), 4.77 (1H, t), 6.62 (1H, v br s), 7.03 (1H, d), 7.39 (1H, t), 7.50 (1H, d), 7.68 (1H, s)
93	ex 27	107-108	1.33 (9H, s), 2.10-2.26 (1H, m), 2.42-2.54 (1H, m), 3.65-3.93 (4H, m), 4.62 (1H, br s), 5.07 (1H, dd), 5.29 (1H, dd), 5.37 (1H, dd), 5.91-6.08 (1H, m), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.57 (1H, dd), 7.69 (1H, br s)
94	ex 26	141-143	1.58 (9H, s), 1.95-2.10 (1H, m), 2.63-2.75 (1H, m), 3.00 (3H, s), 3.78-3.85 (2H, m), 5.63 (1H, br s), 6.54 (1H, dd), 6.94 (1H, br d), 7.36 (1H, t), 7.44 (1H, dt), 7.60 (1H, t)

No.	Prep	mpt	nmr
95	ex 26	141-144	1.59 (9H, s), 1.97-2.14 (1H, m), 2.65-2.77 (1H, m), 3.82-3.91 (2H, m), 5.63 (1H, br s), 6.68 (1H, dd), 7.42 (1H, br d), 7.51 (1H, t), 7.88 (1H, br d), 7.95 (1H, br s)
96	ex 5	115-116	0.98 (3H, t), 1.07 (9H, s), 1.61-1.79 (2H, m), 2.27 (2H, s), 2.30-2.55 (2H, m), 3.30-3.50 (2H, m), 3.75 (1H, q), 3.91-4.01 (1H, m), 4.05 (1H, t), 6.94-7.01 (1H, m), 7.34 (1H, t), 7.55-7.67 (2H, m)
97	ex 5	87-88	1.08 (9H, s), 1.29 (3H, t), 2.28 (2H, s), 2.34-2.53 (2H, m), 3.39-3.61 (2H, m), 3.76 (1H, q), 3.91-4.01 (1H, m), 4.12 (1H, t), 6.95-7.02 (1H, m), 7.36 (1H, t), 7.60 (1H, dd), 7.66 (1H, br s)
98	ex 16	111.5-112.5	0.88 (3H, t), 1.29 (3H, t), 1.32 (6H, s), 1.82 (2H, q), 2.23-2.53 (2H, m), 3.12-3.35 (2H, m), 3.67-3.90 (2H, m), 4.34 (1H, br s), 4.68 (1H, dd), 6.96-7.04 (1H, m), 7.36 (1H, t), 7.58 (1H, dd), 7.68 (1H, br s)
99	ex 23	144-146	1.35 (9H, s), 2.14-2.31 (1H, m), 2.51-2.64 (1H, m), 3.74-3.90 (2H, m), 3.95 (1H, d), 4.15-4.32 (2H, m), 4.93 (1H, dd), 5.23 (1H, br s), 7.41 (1H, br d), 7.50 (1H, t), 7.85-7.94 (2H, m)
100	ex 26	140-142	1.58 (9H, s), 1.95-2.13 (1H, m), 2.63-2.76 (1H, m), 3.01 (3H, s), 3.78-3.86 (2H, m), 5.62 (1H, br s), 6.65 (1H, dd), 7.01-7.08 (1H, m), 7.40 (1H, t), 7.55 (1H, dd), 7.70 (1 H, br s)
101	ex 27	111.5-112.5	1.61(6H, 2s), 2.11-2.29 (1H, m), 2.31 (1H, s), 2.47-2.61 (1H, m), 3.22 (1H, dd), 3.36 (1H, dd), 3.50 (3H, s), 3.56 (3H, s), 3.70-3.90 (2H, m), 4.72 (1H, dd), 4.90 (1H, dd), 6.61 (1H, s), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.55 (1H, dd), 7.68 (1H, br s)
102	ex 5	69-71	1.08 (9H, s), 2.30-2.40 (3H, m), 2.40-2.57 (2H, m), 3.71-3.98 (2H, m), 4.12-4.32 (2H, m), 4.88 (1H, t), 6.97-7.06 (1H, m), 7.37 (1H, t), 7.58 (1H, dd), 7.66 (1H, br s)

No.	Prep	mpt	nmr
103	ex 5	91-93	1.07 (9H, s), 2.26 (2H, d), 2.31-2.56 (2H, m), 3.74 (1H, q), 3.87-3.97 (1H, m), 3.97-4.21 (2H, m), 4.40 (1H, t), 5.28 (1H, dd), 5.36 (1H, dd), 5.81-5.97 (1H, m), 6.95-7.02 (1H, m), 7.35 (1H, t), 7.54-7.68 (2H, m),
104	ex 5	gum	0.98 (3H, t), 2.07 (9H, s), 1.61-1.80 (2H, m), 2.27 (2H, s), 2.33-2.56 (2H, m), 3.30-3.51 (2H,m), 3.78 (1H, q), 3.94-4.08 (2H, m), 7.35 (1H, br d), 7.45 (1H, t), 7.87-7.95 (2H, m)
105	ex 27	137-138.5	0.97 (3H, t), 1.35 (9H, s), 1.55-1.83 (2H, m), 2.30-2.50 (2H, m), 3.02-3.24 (2H, m), 3.70-3.81 (1H, m), 3.84-3.95 (1H, m), 4.40 (1H, br s), 4.46-4.55 (1H t), 7.37 (1H, d), 7.43-7.40 (1H, t), 7.88-7.95 (2H, m)
106	ex 27	84-87	0.96 (3H, t), 1.35 (9H, s), 1.54-1.81 (2H, m), 2.27-2.49 (2H, m), 3.02-3.23 (2H, m), 3.65-3.76 (1H, m), 3.80-3.90 (1H m), 4.41 (1H, br s), 4.55 (1H, t), 6.53 (1H, t), 6.89 (1H, dd), 7.33 (1H, t), 7.46 (1H, dd), 7.61 (1H, t)
107	ex 26	100-107	0.95 (3H, t), 1.58 (9H, s), 1.58-1.70 (1H, m), 1.80-1.98 (1H, m), 2.05-2.21 (1H, m), 2.58-2.70 (1H, m), 3.16-3.43 (2H, m), 3.74-3.89 (2H, m), 5.76 (1H, br s), 6.41 (1H, dd), 6.54 (1H, t), 6.94 (1H, dd), 7.36 (1H, t), 7.44 (1H, dd), 7.60 (1H, t)
108	ex 27	107-109	1.33 (9H, s), 2.11-2.29 (1H, m), 2.42-2.56 (1H, m), 3.66-3.95 (4H, m), 4.61 (1H, br s), 5.05 (1H, dd), 5.26-5.41 (2H, m), 5.92-6.08 (1H, m), 7.40 (1H, d), 7.49 (1H, t), 7.88-7.95 (2H, m)
109	ex 26	148.5-150	1.53 (9H, s), 1.95-2.15 (1H, m), 2.64-2.77 (1H, m), 3.78-3.94 (3H, m), 4.02-4.15 (1H, m), 5.35 (1H, d), 5.40 (1H, br s), 5.99-6.16 (2H, m), 6.71 (1H, dd), 7.41 (1H, d), 7.50 (1H, t), 7.88 (1H, d), 7.93 (1H, br s)

No.	Prep	mpt	nmr
110	ex 5	gum	1.06 (9H, s), 2.23 (1H, d), 2.31 (1H, d), 2.33-2.45 (2H, m), 3.74 (1H, q), 3.85-4.20 (3H, m), 4.41 (1H, t), 5.23-5.40 (2H, m), 5.81-5.96 (1H, m), 6.51 (1H, t), 6.89 (1H, dd), 7.32 (1H, t), 7.46 (1H, dd), 7.58 (1H, t)
111	ex 27	gum	1.32 (9H, s), 2.05-2.25 (1H, m), 2.40-2.53 (1H, m), 3.64-3.92 (3H, m), 4.61 (1H, br s), 5.07 (1H, dd), 5.25-5.41 (2H, m), 5.91-6.06 (1H, m), 6.53 (1H, t), 6.90 (1H, dd), 7.34 (1H, t), 7.44 (1H, dt), 7.60 (1H, t)
112	ex 26	130-132	1.51 (9H, s), 1.93-2.11 (1H, m), 2.62-2.75 (1H, m), 3.73-4.14 (4H, m), 5.30-5.42 (2H, m), 6.00-6.16 (2H, m), 6.70 (1H, dd), 7.01 (1H, dd), 7.38 (1H, t), 7.54 (1H, dd), 7.68 (1H, br s)
113	ex 5	solid gum	3:1 Rotamer mixture : 1.06 (9H, 2s), 2.20-2.60 (4H, m), 2.75-2.90 (7H, m), 3.15-3.30 (1H, m), 3.40-3.56 (1H, m), 3.72-3.88 (2H, m), 3.90-4.10 (1H, m), 4.35 and 4.85 (1H, 2t), 6.99-7.10 (1H, m), 7.31-7.67 (3H, m)
114	ex 26	108-109	1.34 (3H, t), 1.60 (9H, s), 2.02-2.20 (1H, m), 2.60-2.74 (1H, m), 3.29-3.60 (2H, m), 3.74-3.88 (2H, m), 5.74 (1H, br s), 6.53 (1H, dd), 6.98-7.05 (1H, m), 7.49 (1H, t), 7.54 (1H, dd), 7.68 (1H, br s)
115	ex 26	142-143	1.45 (9H, s), 1.90-2.10 (1H, m), 3.07-3.25 (1H, m), 3.75-3.84 (2H, m), 4.90-5.06 (1H, m), 6.54 (1H, br d), 6.65 (1H, v br s), 7.05 (1H, dd), 7.40 (1H, t), 7.45-7.56 (1H, m), 7.70 (1H, s)
116	ex 27	172-173.5	0.97 (3H, t), 1.65 (6H, 2s), 1.65-1.81 (1H, m), 2.31 (1H, s), 2.32-2.48 (2H, m), 3.08-3.22 (2H, m), 3.74 (1H, q), 3.81-3.93 (1H, m), 4.52 (1H, t), 4.68 (1H, br s), 6.95-7.04 (1H, m), 7.37 (1H, t), 7.57 (1H, dd), 7.67 (1H, s)
117	ex 28	129-131	1.38 (9H, s), 2.10 (3H, s), 2.13-2.32 (1H, m), 2.40-2.55 (1H, m), 3.38 (2H, t), 3.67-3.90 (2H, m), 4.30 (2H, t), 4.81 (1H, dd), 5.43 (1H, s), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.57 (1H, dd), 7.67 (1H, br s)

No.	Prep	mpt	nmr
118	ex 16	114.5-116	10:1 Rotamer mixture, major rotamer: 0.86 (3H, t), 0.95 (3H, t), 1.29 (6H, s), 1.51-1.82 (4H, m), 2.27-2.50 (2H, m), 3.00-3.25 (2H, m), 3.65-3.91 (2H, m), 4.32 (1H, br s), 4.53 (1H, t), 6.93-7.05 (1H, m), 7.36 (1H, t), 7.50-7.71 (2H, m)
119	ex 23	130.5-132.5	1.35 (9H, s), 2.13-2.31 (1H, m), 2.49-2.63 (1H, m), 3.70-3.90 (5H, m), 3.91 (1H, d), 4.02 (1H, d), 4.90 (1H, dd), 5.20 (1H, s), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.55 (1H, dd), 7.64-7.68 (1H, m)
120	ex 27	105-107.5	0.97 (3H, t), 1.20-1.46 (11H, m), 1.48-1.78 (2H, m), 2.27-2.50 (2H, m), 3.04-3.27 (2H, m), 3.66-3.78 (1H, m), 3.82-3.91 (1H, m), 4.42 (1H, s), 4.54 (1H, t), 6.95-7.02 (1H, m), 7.35 (1H, t), 7.57 (1H, dd), 7.68 (1H, br s)
121	ex 27	117-118.5	1.34 (9H, s), 2.10-2.26 (1H, m), 2.44-2.56 (1H, m), 3.25-3.43 (2H, m), 3.43 (3H, s), 3.54-3.62 (1H, m), 3.66-3.88 (3H, m), 4.89 (1H, dd), 6.35 (1H, s), 6.96-7.04 (1H, m), 7.37 (1H, t), 7.57 (1H, dd), 7.68 (1H, br s)
122	ex 27	106-107.5	1.36 (9H, s), 2.23 (3H, s), 2.28-2.54 (2H, m), 2.80 (1H, t), 3.35-3.54 (2H, m), 3.68-3.93 (2H, m), 4.54 (1H, t), 5.19 (1H, s), 7.01 (1H, br d), 7.37 (1H, t), 7.57 (1H, dd), 7.67 (1H, br s)
128	ex 29	gum	1.62 (9H, s), 2.13-2.27 (1H, m), 2.50-2.63 (1H, m), 3.75 (1H, d), 3.84-3.97 (3H, m), 5.03 (1H, dd), 7.41-7.56 (2H, m), 7.85-7.94 (2H, m)
199			* 7.9(1H,m); 7.6(1H,m); 7.2-7.3(2H,m); 5.95-6.1(1H,m); 5.8-5.95(1H,m); 5.25-5.4(2H,m); 4.9-5.05(2H,m); 4.4(1H,t); 3.9-4.2(2H,m); 3.85-3.9(1H,m); 3.7-3.8(1H,q); 2.3-2.5(4H,m); 1.2(6H,d).
200		92-94	* 7.9(1H,m); 7.6(1H,m); 7.2-7.3(2H,m); 5.9-6.1(1H,m); 5.25-5.45(2H,m); 5.1(1H,m); 4.55(1H,s); 3.7-3.9(4H,m); 2.4-2.55(1H,m); 2.1-2.3(1H,m); 1.3(9H,s).

No.	Prep	mpt	nmr
201			* 7.9(1H,m); 7.6(1H,m); 7.2-7.3(2H,m); 5.8-6.0(1H,m); 5.2-5.4(2H,m); 4.4(1H,t); 3.95-4.2(2H,m); 3.85-3.95(1H,m); 3.7-3.8(1H,m); 2.35 2.45(2H,m); 2.25(2H,d); 1.1(9H,s).
202		136.0-138.0	7.7(1H,s); 7.5(1H,m); 7.4(1H,t); 7.0(1H,m); 5.05(1H,m); 4.4-4.5(1H,m); 3.8(2H,m); 2.9(3H,s); 2.85-2.95(1H,m); 1.9-2.1 (1H,m); 1.4(9H,s).
203			7.85(2H,m); 7.2-7.5(7H,m); 5.0(1H,m); 4.6(2H,s); 4.5(1H,m); 3.8(2H,m); 2.75-2.9(1H,m); 1.85-2.0(1H,m); 1.5(9H,s).
204			8.0(1H,s); 7.9(1H,m); 7.4-7.6(2H,m); 5.1(1H,m); 4.5(1H,m); 3.8-4.0(4H,m); 2.9-3.0(1H,m); 1.9-2.1(1H,m); 1.3(12H,m).
205		164	1.09(9H,s); 2.0(1H,m); 2.15(2H,s); 2.9(1H,m); 3.8(2H,m); 4.55(1H,m); 6.1(1H,m); 7.1(1H,t); 7.5(1H,m); 7.8(1H,m).
206		173	1.3(9H,s); 2.0(1H,m); 2.8(1H,m); 3.8(2H,m); 4.4(1H,m); 4.85(1H,s); 5.2(1H,d); 7.1(1H,t); 7.45(1H,m); 7.75(1H,m).
207		137	1.35(9H,s); 2.1(1H,m); 2.45(1H,m); 2.83(3H,s); 3.75(2H,m); 4.42(1H,s); 5.2(1H,m); 7.1(1H,t); 7.5(1H,m); 7.8(1H,m).
208		87	1.1(9H,s); 2.1-2.5(1H,m); 2.3(2H,m); 3.1(3H,s); 3.8(2H,m); 7.1(1H,t); 7.5(1H,m); 7.8(1H,m).
209		103	1.3(9H,s); 2.2(1H,m); 2.45(1H,m); 3.6-3.9(4H,m); 4.6(1H,s); 5.0(1H,m); 5.3(2H,m); 6.0(1H,m); 7.1(1H,t); 7.5(1H,m); 7.8(1H,m).
210			.05(9H,s); 2.25(2H,s); 2.4(2H,m); 3.7(1H,q); 3.9(1H,m); 4.1(2H,m); 4.3(1H,t); 5.3(2H,m); 5.9(1H,m); 7.3(1H,t); 7.5(1H,m); 7.8(1H,m).
211		115	1.15(3H,s); 1.16(3H,s); 1.9(1H,m); 2.3(2H,s); 2.85(1H,m); 3.8(2H,m); 4.5(1H,m); 5.1(2H,m); 5.95(1H,m); 6.2(1H,m); 7.15(1H,t); 7.5(1H,m); 7.8(1H,m).

No.	Prep	mpt	nmr
212			1.2(6H,s); 2.2(1H,m); 2.4(3H,m); 3.05(3H,s); 3.8(2H,m); 4.9-5.2(3H,m); 6.0(1H,m); 7.1(1H,t); 7.5(1H,m); 7.8(1H,m).
213		93	1.1(9H,s); 1.3(3H,t); 2.3(2H,s); 2.45(2H,m); 3.5(2H,m); 3.8(1H,q); 4.0(1H,m); 4.1(1H,t); 7.4(2H,m); 7.9(2H,m).
214		75	0.85(3H,t); 1.05(3H,s); 1.06(3H,s); 1.3(3H,t); 1.4(2H,q); 2.25(2H,s); 2.45(2H,m); 3.5(2H,m); 3.8(1H,q); 4.0(1H,m); 4.1(1H,t); 7.4(2H,m); 7.9(2H,m).
215			1.12(9H,s); 2.30-2.53(2H,m); 2.63(2H,s); 3.81-4.02(2H,m); 5.39-5.47(1H,t); 7.00-7.04(1H,m); 7.35-7.41(1H,t); 7.55-7.62(2H,m); 9.28(1H,s).
216			.11(9H,s); 2.30-2.55(2H,m); 2.63(2H,s); 3.85-4.05(2H,m); 5.40-5.48(1H,t); 7.40-7.52(2H,m); 7.84-7.94(2H,m); 9.28(1H,s).
217			0.84-0.91(3H,t); 1.01(6H,s); 1.34-1.44(2H,q); 1.91-2.07(1H,m); 2.02(2H,s); 2.88-2.99(1H,m); 3.81-3.90(2H,m); 4.51-4.60(1H,m); 6.08(1H,s); 7.40-7.54(2H,m); 7.87-7.93(2H,m).
218			0.84-0.90(3H,t); 1.03-1.04(6H,d); 1.40-1.48(2H,q); 2.13-2.29(1H,m); 2.30-2.32(2H,d); 2.42-2.54(1H,m); 3.09(3H,s); 3.78-3.95(2H,m); 5.15-5.23(1H,t); 7.39-7.53(2H,m); 7.89-7.93(2H,m).
219			0.84-0.90(3H,t); 1.03(6H,d); 1.39-1.47(2H,q); 2.10-2.27(1H,m); 2.29-2.34(2H,d); 2.40-2.52(1H,m); 3.07(3H,s); 3.73-3.92(2H,m); 5.18-5.25(1H,t); 7.00-7.04(1H,m); 7.34-7.41(1H,t); 7.54-7.60(1H,m); 7.67(1H,s).

No.	Prep	mpt	nmr
220			0.86-0.91(3H,t); 1.32(6H,s); 1.68-1.76(2H,q); 2.16-2.29(1H,m); 2.69-2.80(1H,m); 3.80-3.86(2H,m); 4.30-4.36(1H,t); 5.54(1H,s); 7.20-7.32(2H,m); 7.58-7.63(1H,m); 7.80-7.82(1H,m).
221			1.07(9H,s); 1.87-2.04(1H,m); 2.14(2H,s); 2.84-2.95(1H,m); 3.77-3.83(2H,m); 4.50-4.60(1H,m); 6.05-6.11(1H,d); 7.21-7.33(2H,m); 7.58-7.62(1H,m); 7.83-7.85(1H,m);
222			0.84-0.91(3H,t); 1.00-1.04(6H,d); 1.34-1.43(2H,q); 1.8702.05(1H,m); 2.13(2H,s); 2.85-2.96(1H,m); 3.77-3.84(2H,m); 4.48-4.57(1H,m); 6.06(1H,d); 7.22-7.33(2H,m); 7.58-7.62(1H,m); 7.83-7.86(1H,m).
223			0.84-0.90(3H,t); 1.28-1.30(6H,d); 1.65-1.74(2H,q); 1.90-2.04(1H,m); 2.78-2.90(1H,m); 3.74-3.82(2H,m); 4.35-4.44(1H,m); 4.58(1H,s); 4.94-4.98(1H,d); 7.21-7.33(2H,m); 7.57-7.61(1H,m); 7.82-7.84(1H,m).
224			1.20(6H,s); 2.05-2.22(1H,m); 2.36-2.50(3H,m); 3.03(3H,s); 3.71-3.89(2H,m); 4.94-5.03(2H,m); 5.18-5.26(1H,t); 5.96-6.06(1H,m); 7.19-7.31(2H,m); 7.59-7.63(1H,m); 7.84-7.86(1H,m).
225			1.16-1.18(6H,d); 1.85-2.01(1H,m); 2.29(2H,s); 2.83-2.93(1H,m); 3.77-3.82(2H,m); 4.48-4.57(1H,m); 5.03-5.11(2H,m); 5.90-6.00(1H,m); 6.13-6.18(1H,d); 7.22-7.33(2H,m); 7.58-7.62(1H,m); 7.83-7.85(1H,m).
226			1.16-1.19(6H,d); 1.91-2.04(1H,m); 2.29(2H,s); 2.85-2.96(1H,m); 3.81-3.89(2H,m); 4.50-4.60(1H,m); 5.03-5.11(2H,m); 5.90-6.00(1H,m); 6.18-6.22(1H,d); 7.41-7.54(2H,m); 7.86-7.93(2H,m).

No.	Prep	mpt	nmr
227			1.20(6H,s); 2.09-2.25(1H,m); 2.41-2.42(2H,d); 2.40-2.51(1H,m); 3.04(3H,s); 3.73-3.91(2H,m); 4.93-5.03(2H,m); 5.17-5.24(1H,t); 5.95-6.05(1H,m); 7.00-7.05(1H,m); 7.34-7.41(1H,t); 7.54-7.59(1H,m); 7.66(1H,s).
228			1.10(9H,s); 2.05-2.52 4(m) 3.06(s,3H)+2.88 (s); 3.73-3.90(2H,m); 5.20-5.28(1H,t);+4.83-4.91 (t); 7.59-7.63(1H,m); 7.85-7.87(1H,m).
229			.38(9H,s); 2.02-2.17(1H,m); 2.41-2.52(1H,m); 2.83(3H,s); 3.69-3.83(2H,m); 4.44(1H,s); 5.18-5.26(1H,m); 7.20-7.30(2H,m); 7.60-7.64(1H,m); 7.84-7.86(1H,m).
230			0.84-0.91(3H,t); 1.03-1.05(6H,d); 1.40-1.48(2H,q); 2.05-2.51(2H,m); 2.29-2.32(2H,d); 3.06(3H,s)+ 2.86(s); 3.72-3.90(2H,m); 5.19-5.26(1H,t)+4.84-4.92(t); 7.20-7.30(2H,m); 7.59-7.63(1H,m); 7.84-7.87(1H,m).
231			1.33(9H,s); 1.90-2.09(1H,m); 2.78-2.90(1H,m); 3.74-3.81(2H,m); 4.36-4.46(1H,m); 4.70(1H,s); 4.97-5.00(1H,m); 7.20-7.32(2H,m); 7.55-7.60(1H,m); 7.82-7.84(1H,m).
232			.38(9H,s); 2.15-2.29(1H,m); 2.69-2.81(1H,m); 3.81-3.87(2H,m); 4.30-4.37(1H,t); 5.67(1H,s); 7.20-7.31(2H,m); 7.59-7.63(1H,m); 7.80-7.82(1H,m).
233			2.11-2.25(1H,m); 2.42(3H,s); 2.69-2.81(1H,m); 3.84-3.90(2H,m); 4.38-4.44(1H,t); 7.21-7.33(2H,m); 7.59-7.64(1H,m); 7.80-7.82(1H,m).
305	ex 5	126-127	1.96 (3H, s), 1.90-2.10 (1H, m), 2.20 (3H, s), 2.85-2.98 (1H, m), 3.77-3.86 (2H, m), 4.55-4.65 (1H, m), 5.65 (1H, t), 6.17 (1H, br d), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.53 (1H, dd), 7.68 (1H, br s)

No.	Prep	mpt	nmr
306	ex 5	163.5-164.5	0.94-1.04 (6H, m), 1.88-2.21 (4H, m), 2.85-2.98 (1H, m), 3.77-3.88 (2H, m), 6.20 (1H, br d), 7.01-7.09 (1H, m), 7.40 (1H, t), 7.53 (1H, dd), 7.68 (1H, br s)
307	ex 5	106-107.5	0.88 (3H, t), 1.01 (6H, s), 1.39 (2H, q), 1.87-2.05 (1H, m), 2.14 (2H, s), 2.85-2.96 (1H, m), 3.82 (1H, dd), 4.50-4.60 (1H, m), 6.13 (1H, br d), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.50-7.57 (1H, m), 7.68 (1H, br s)
308	ex 90	gum	3:2 Rotamer mixture : 2.21-2.45 (1H, m), 2.46-2.63 (1H, m), 3.08 (3H, s), 3.80-3.95 (2H, m), 4.75-4.96 (1H, 2m), 4.78 (2H, s), 7.43 (1H, d), 7.51 (1H, t), 7.88-7.92 (2H, m)
309	ex 20	89-92	1.38 (9H, s), 2.16-2.30 (1H, m), 2.68-2.83 (1H, m), 3.79-3.90 (2H, m), 4.35 (1H, t), 5.67 (1H, br s), 6.53 (1H, t), 6.84 (1H, dd), 7.36 (1H, t), 7.44 (1H, dt), 7.56 (1H, t)
310	ex 5	gum	3:1 Rotamer mixture : 2.19-2.38 (1H, m), 2.49-2.64 (1H, m), 3.01 (0.75H, s), 3.24 (2.25H, t), 3.78-3.98 (2H, m), 5.00-5.15 (1H, m), 7.02-7.10 (1H, m), 7.36-7.46 (1H, m), 7.52-7.60 (1H, m), 7.66 (1H, br s)
311	ex 89	153-154	1.37 (9H, s), 2.06-2.25 (1H, m), 2.35-2.50 (1H, m), 3.22-3.51 (4H, m), 3.71-3.87 (2H, m), 4.84 (1H, dd), 6.96-7.06 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.71 (1H, br s)
312	ex 27	89-91	0.85 (3H, t), 1.28 (6H, s), 1.68 (2H, q), 2.08-2.25 (1H, m), 2.40-2.54 (1H, m), 3.66-3.95 (4H, m), 4.53 (1H, br s), 5.05 (1H, dd), 5.29 (1H, dd), 5.38 (1H, dd), 5.91-6.08 (1H, m), 6.96-7.04 (1H, m), 7.37 (1H, t), 7.57 (1H, dd), 7.69 (1H, br s)
313	ex 5	117-119	1.06 (9H, d), 1.86-2.03 (1H, m), 2.15 (2H, s), 2.85-2.96 (1H, m), 3.82 (1H, dd), 4.50-4.61 (1H, m), 6.10 (1H, br d), 6.54 (1H, t), 6.94 (1H, dd), 7.36 (1H, t), 7.44 (1H, dt), 7.59 (1H, t)

No.	Prep	mpt	nmr
314	ex 20	gum	1.66 (6H, s), 2.16-2.31 (1H, m), 2.38 (1h, s), 2.70-2.85 (1H, m), 3.80-3.90 (2H, m), 4.38 (1H, t), 6.19 (1H, br s), 6.54 (1H, t), 6.94 (1H, br d), 7.35 (1H, t), 7.44 (1H, dt), 7.55 (1H, t)
315	ex 90	84 (dec)	3:1 Rotamer mixture : 1.96 (6H, s), 2.17-2.38 (1H, m), 2.43-2.55 (1H, m), 2.94 and 2.97 (3H, 2s), 3.72-3.91 (2H, m), 4.84-4.98 (1H, m), 7.04 (1H, br d), 7.40 (1H, t), 7.57 (1H, dd), 7.68 (1H, br s)
316	ex 27	122-123	1.35 (9H, s), 1.51 (9H, s), 2.15-2.30 (1H, m), 2.47-2.60 (1H, m), 3.70-3.85 (4H, m), 4.96 (1H, dd), 5.14 (1H, br s), 7.02 (br d), 7.39 (1H, t), 7.55 (1H, dd), 7.71 (1H, br s)
317	ex 27	149-151	1.22 (9H, s), 1.31 (9H, s), 2.02-2.18 (1H, m), 2.47-2.60 (1H, m), 3.68-3.85 (1H, m), 4.20 (1H, d), 4.38 (1H, d), 4.66-4.78 (2H, m), 6.99-7.06 (1H, m), 7.39 (1H, t), 7.52-7.57 (1H, m), 7.67 (1H, br s)
318	ex 27	113.5-114.5	1.36 (9H, s), 2.30-2.48 (1H, m), 2.64-2.77 (1H, m), 3.78-3.96 (2H, m), 4.15 (1H, d), 4.30 (1H, d), 4.73 (1H, dd), 5.07 (1H, br s), 7.08 (1H, dd), 7.43 (1H, t), 7.50-7.58 (1H, m), 7.64 (1H, br s)
319	ex 20	132.5-134	0.93 (9H, s), 2.08-2.26 (1H, m), 2.41-2.55 (1H, m), 2.92 (3H, s), 3.08 (2H, d), 3.71-3.90 (2H, m), 4.64 (1H, br t), 5.15 (1H, dd), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.57 (1H, dd), 7.70 (1H, br s)
320	ex 20	oil	1.07 (9H, s), 2.24 (1H, d), 2.31 (1H, d), 2.34-2.47 (2H, m), 3.77 (1H, q), 3.90-4.04 (1H, m), 4.04-4.21 (2H, m), 4.37 (1H, t), 5.28 (1H, dd), 5.36 (1H, dd), 5.82-5.98 (1H, m), 7.37 (1H, br d), 7.46 (1H, t), 7.96-7.95 (1H, m)
321	ex 90	73-75	3:2 Rotamer mixture : 2.18-2.43 (1H, m), 2.43-2.63 (1H, m), 3.06 (3H, s), 3.74-3.92 (2H, m), 4.72-5.00 (3H, m), 7.00-7.09 (1H, m), 7.40 (1H, t),.7.56 (1H, br t), 7.68 (1H, br s)

No.	Prep	mpt	nmr
322	ex 5	128-131	1.09 (9H, s), 1.29 (3H, t), 2.28 (2H, s), 2.32-2.52 (2H, m), 3.40-3.62 (2H, m), 3.75 (1H, q), 3.90-4.01 (1H, m), 4.15 (1H, t), 6.52 (1H, t), 6.89 (1H, dd), 7.33 (1H, t), 7.48 (1H, dd), 7.60 (1H, t)
323	ex 20	143-147	1.26 (3H, s), 1.36 (9H, s), 2.21-2.52 (2H, m), 3.10-3.36 (2H, m), 3.65-3.90 (2H, m), 4.44 (1H, br s), 4.70 (1H, dd), 6.54 (1H, t), 6.90 (1H, dd), 7.34 (1H, t), 7.42-7.48 (1H, m), 7.61 (1H, t)
324	ex 5	gum	1.08 (9H, s), 2.20 (1H, d), 2.40 (1H, d), 2.50 (2H, q0, 3.72-4.08 (4H, m), 4.30-4.47 (1H, m), 6.97-7.04 (1H, m), 7.37 (1H, t), 7.55-7.65 (2H, m)
325	ex 5	gum	10:1 Rotamer mixture : 2.10-2.30 (1H, m), 2.41-2.57 (1H, m), 2.79-3.20 (7H, m), 3.75-3.94 (2H, m), 4.81 and 5.20 (1H, 2dd), 7.01-7.10 (1H, m), 7.40 (1H, t), 7.54-7.70 (2H, m)
326	ex 88	65.5-67.5	5:2 Rotamer mixture : 2.19-2.39 (1H, m), 2.50-2.65 (1H, m), 3.00 (6/7H, s), 3.24 (15/7H, t), 3.78-3.98 (2H, m), 5.0-5.16 (1H, m), 7.02-7.13 (1H, m), 7.36-7.47 (1H, m), 7.53-7.61 (1H, m), 7.65 (1H, br s)
327	ex 20	128-130	1.34 (9H, s), 2.40-2.52 (1H, m), 3.70-3.94 (3H, m), 4.05-4.23 (1H, m), 4.31 (1H, t), 4.77 (1H, br s), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.56 (1H, t), 7.56 (1H, dd), 7.65 (1H, br s)
328	ex 87	gum	10:1 Rotamer mixture : 2.08-2.28 (1H, m), 2.40-2.80 (5H, m), 2.91 and 3.05 (3H, 2s), 3.73-3.93 (2H, m), 4.75 and 5.20 (1H, 2dd), 6.99-7.10 (1H, m), 7.35-7.45 (1H, m), 7.52-7.60 (1H, m), 7.66 (1H, br s)
329	ex 35	107-109	1.34 (9H,s), 4.72 (1H, d), 4.90 (1H, br s), 5.08 (1H, dd), 6.21 (1H, d), 7.72 (2H, s+d), 7.94 (1H, d)
330	ex 35	151-153	1.34 (9H, s), 4.74 (1H, d), 4.88 (1H, br s), 5.11 (1H, dd), 6.22 (1H, d), 7.55 (1H, dd), 7,92 (1H, d), 8.00 (1H, d)

No.	Prep	mpt	nmr
331	ex 35	118-119	1.35 (9H, s), 4.59 (1H, d), 4.90 (2H, dd +br s), 6.01 (2H, s), 6.18 (1H, d), 6.83 (2H, m), 6.99 (1H, d)
332	ex 62/67	77-78	1.35 (9H, s), 2.2(1H, m), 2.8 (1H, m), 3.9 (3H, s), 4.0 (1H, m), 4.3 (1H, m), 4.9 (1H, br s), 5.5 (1H, t), 8.15 (1H, s)
333	ex 62/67	190	1.35 (9H, s), 2.2 (1H, m), 2.8 (1H, m), 4.0 (1H, m), 4.3 (1H, m), 4.9 (1H, br s), 5.5(1H, t), 7.8 (1H, s)
339	ex 62/66	gum	1.35(9H,s); 2.15(1H,m); 2.7(1H,m); 3.8(1H,m); 4.2(1H,m); 4.95(1H,br s); 5.4(1H,t); 7.30(1H,t); 7.40(1H,t); 7.8(1H,s).
282		92.6-93.4	0.15(9H,s); 2.06(2H,m); 2.14(1H,m); 2.44(1H,m); 2.99(3H,s); 3.78(2H,m); 5.27(1H,dd); 6.98(1H,m); 7.35(1H,t); 7.55(1H,dd); 7.64(1H,s).
291		98.5-99.5	1.10(9H,s); 1.31(3H,t); 2.30(2H,q); 3.58(2H,m); 4.63(1H,d); 5.23(1H,dd); 5.27(1H,s); 7.51(2H,m); 7.70(1H,m); 7.76(1H,s).
292		104.7-105.7	1.29(3H,t); 1.35(9H,s); 3.31(2H,m); 4.56(1H,s); 4.71(1H,d); 4.99(1H,dd); 5.86(1H,s); 7.52(2H,m); 7.70(1H,m); 7.79(1H,s).
293		oil	1.01(3H,t); 1.06(9H,s); 1.71(2H,sextet); 2.28(2H,q); 3.45(2H,dt); 4.61(1H,d); 5.20(2H,m); 7.48-7.55(2H,m); 7.70(1H,m); 7.76(1H,s).
294		115.7-116.7	0.96(3H,t); 1.31(9H,s); 1.70(2H,sextet); 3.19(2H,dd); 4.54(1H,s); 4.70(1H,d); 5.01(1H,dd); 5.70(1H,s); 7.50(2H,m); 7.69(1H,m); 7.79(1H,s).
295		62.0-63.8	1.06(9H,s); 2.27(2H,dd); 4.26(2H,m); 4.62(1H,d); 5.17(1H,dd); 5.31(1H,s); 5.32(1H,br s); 5.43(1H,d); 5.89(1H,m); 7.50(2H,m); 7.67(1H,m); 7.75(1H,s).
296		121.5-122.5	1.30(9H,s); 3.88(2H,m); 4.73(2H,d); 4.93(1H,dd); 5.30(1H,dd); 5.41(1H,dd); 5.96(1H,m); 6.13(1H,s); 7.52(2H,m); 7.70(1H,m); 7.76(1H,s).

No.	Prep	mpt	nmr
297		91-92	1.08(9H,s); 2.36(2H,q); 2.45(1H,s); 4.30(2H,dq); 4.68(1H,d); 5.15(1H,d); 5.61(1H,s); 7.51(2H,m); 7.69(1H,m); 7.74(1H,s).
298		141.5-142.8	1.33(9H,s); 2.38(1H,t); 4.13(2H,ddd); 4.77(1H,d); 4.96(1H,dd); 5.27(1H,s); 6.13(1H,s); 7.53(2H,m); 7.70(1H,m); 7.78(1H,s).
126		94.5-96	1.08(9H,s); 2.30(1H,d); 2.41(1H,d); 3.84(3H,s); 4.65(1H,d); 5.19(1H,dd); 5.80(1H, br s); 7.52-7.78(4H,m).
299		128.5-129.5	3.71(3H,s); 5.11(2H,s); 7.40(1H, br s); 7.49-7.71(4H,s); 7.82(1H,s).
300		111.3-111.8	0.89(9H,s); 3.02(2H,d); 3.95(2H,m); 4.71(1H,d); 4.84(1H,t); 5.01(1H,dd); 5.34(1H,m); 5.50(1H,m); 5.92(1H,s); 6.00(1H,m); 7.50(2H,m); 7.70(1H,m); 7.77(1H,s).
301		145-145.5	0.91(9H,s); 2.43(1H,t); 3.08(2H,m); 4.11(1H,dd); 4.24(1H,dd); 4.74(1H,d); 5.00(1H,dd); 5.32(1H,t); 5.99(1H,s); 7.50(2H,m); 7.75(2H,m).
302		96-98	1.43(6H,s); 2.39(1H,t); 3.79(2H,s); 4.10(1H,dd); 4.25(1H,dd); 4.77(1H,d); 4.97(1H,dd); 5.47(1H,s); 6.10(1H,s); 7.54(2H,m); 7.72(1H,m); 7.78(1H,s).
303		199.5-201	1.62(9H,s); 3.77(1H,d); 3.99(1H,d); 4.84(1H,d); 4.91(1H,dd); 6.17(1H,s); 7.56(2H,m); 7.74(2H,m).
304		149.6-150.6	1.37(9H,s); 4.74(1H,d); 5.01(1H,dd); 5.47(1H,s); 5.58(1H,s); 7.51-7.72(3H,m); 7.76(1H,s).
125		116-117	1.10(9H,s); 2.31(2H,s); 3.14(3H,s); 4.74(1H,d); 5.04(1H,dd); 6.10(1H,br s); 7.55(2H,m); 7.75(2H,m).
124		139-140	1.37(9H,s); 2.88(3H,s); 4.55(1H,br s); 4.79(1H,d); 4.88(1H,dd); 6.38(1H,s); 7.55(2H,m); 7.72(1H,m); 7.80(1H,m).
281		115-116	1.60(3H,s); 1.63(3H,s); 2.15(1H,m); 2.50(1H,m); 2.89(3H,s); 3.80(2H,m); 4.70(1H,br s); 5.13(1H,dd); 7.02(1H,m); 7.40(1H,br); 7.56(1H,dd); 7.68(1H,m).
273		91-93	.36(9H,s); 2.69(2H,dq); 4.79(1H,m); 5.46(2H,d); 5.65(1H,br s); 6.56(1H,t); 6.98(1H,m); 7.28(1H,m); 7.39(1H,t); 7.51(1H,t).

No.	Prep	mpt	nmr
277		104-106	1.65(6H,s); 2.35(1H,s); 2.74(2H,dq); 4.80(1H,m); 5.48(2H,d); 6.07(1H,br s); 6.55(1H,t); 6.98(1H,dd); 7.29(1H,m); 7.39(1H,t); 7.51(1H,t).
67		oil	1.35(9H,s); 2.71(2H,dq); 4.80(1H,m); 5.48(2H,s); 5.71(1H,br s); 7.06(1H,m); 7.26(1H,m); 7.40(1H,t); 7.50(1H,s); 7.64(1H,t).
66		gum	1.28(3H,t); 2.95(2H,dq); 4.19(2H,q); 4.80(1H,m); 5.50(2H,s); 7.05(1H,m); 7.28(1H,m); 7.42(1H,t); 7.49(1H,s); 7.63(1H,t).
62		58-59	1.34(3H,t); 2.95(2H,dq); 4.19(2H,q); 4.79(1H,m); 5.48(2H,s); 6.56(1H,t); 6.97(1H,m); 7.29(1H,m); 7.39(1H,t); 7.55(1H,t).
274		94-95	0.92(9H,s); 2.82(2H,dq); 3.10(2H,??); 4.80(1H,m); 5.49(2H,d); 5.95(1H,br s); 6.55(1H,t); 6.97(1H,dd); 7.28(1H,m); 7.39(1H,t); 7.53(1H,t).
275		85-87	0.86(3H,t); 1.30(6H,s); 1.73(2H,q); 2.71(2H,dq); 4.79(1H,m); 5.47(2H,s); 5.54(1H,br s); 6.55(1H,t); 6.97(1H,dd); 7.29(1H,m); 7.39(1H,t); 7.53(1H,t).
276		85-87	1.45(6H,s); 2.72(2H,dq); 4.79(1H,m); 5.07(2H,m); 5.47(2H,d); 5.78(1H,br s); 6.02(1H,m); 6.56(1H,t); 6.98(1H,dd); 7.29(1H,m); 7.39(1H,t); 7.53(1H,t).
278		gum	1.35(3H,d); 3.17(1H,m); 4.88(1H,q); 5.20(2H,ABq); 5.46(1H,m); 5.50(1H,m); 7.34(5H,m); 7.50(2H,m); 7.76(1H,m); 7.80(1H,br s).
279			1.46(3H,d); 3.24(1H,m); 4.54(1H,m); 4.98(1H,d); 5.13(1H,m); 5.24(1H,d); 5.39(1H,m); 7.18(5H,m); 7.47(2H,m); 7.65(2H,m).
280		99-101	1.28(3H,d); 1.37(9H,s); 2.83(1H,dq); 4.75(1H,m); 5.51(2H,d); 5.73(1H,br s); 7.50(2H,m); 7.76(1H,d); 7.85(1H,m).
283		gum	1.08(9H,s); 2.20-2.50(4H,s+m); 3.72(1H,m); 3.91(1H,m); 4.23(1H,t); 4.67(1H,d); 4.79(1H,d); 7.24(2H,m); 7.41(4H,m); 7.90(2H,m).

No.	Prep	mpt	nmr
284		gum	1.19(9H,s); 2.28(1H,m); 2.52(1H,m); 3.80(2H,m); 4.30(1H,s); 4.38(1H,d); 4.54(1H,d); 4.99(1H,m); 7.25(2H,d); 7.41(1H,t); 7.51(3H,m); 7.90(2H,m).
285		gum	1.08(9H,s); 2.30(2H,ABq); 2.39(2H,m); 3.78(1H,m); 3.90(1H,m); 4.37(1H,t); 4.68(1H,d); 4.94(1H,d); 7.25(1H,m); 7.43(2H,m); 7.75(2H,m); 7.90(2H,m); 8.58(1H,m).
286		147-149	1.29(9H,s); 2.34(1H,m); 2.50(1H,m); 3.83(2H,m); 4.48(2H,ABq); 4.98(1H,m); 6.16(1H,s); 7.27(1H,m); 7.40(1H,m); 7.49(1H,m); 7.63(1H,m); 7.75(1H,dt); 7.92(2H,m); 8.55(1H,m).
287		gum	1.09(9H,s); 2.23-2.50(4H,s+m); 3.76(1H,m); 3.93(1H,m); 4.24(1H,t); 4.77(2H,ABq); 7.40(3H,m); 7.88(3H,m); 8.55(2H,m).
288		140-143	1.25(9H,s); 2.29(1H,m); 2.51(1H,m); 3.82(2H,m); 4.38(1H,s); 4.42(1H,d); 4.57(1H,m); 4.94(1H,m); 7.31-7.52(3H,m); 7.88(2H,m); 7.94(1H,m); 8.58(2H,m).
289		gum	1.08(9H,s); 2.24(2H,ABq); 2.39(2H,m); 3.77(1H,m); 3.91(1H,m); 4.33(1H,t); 4.62(1H,d); 4.82(1H,d); 7.38(2H,m); 7.49(2H,m); 7.90(2H,m); 8.64(2H,m).
290		151-153	1.25(9H,s); 2.26(1H,m); 2.54(1H,m); 3.82(2H,m); 4.30(1H,s); 4.38(1H,m); 4.56(1H,m); 4.95(1H,m); 7.37-7.54(4H,m); 7.89(2H,m); 8.65(2H,m).
504			1.35,(9H,s); 2.27 (1H,m); 2.77 (1H,m); 4.15 (1H,q); 4.36 (1H,dt); 4.70 (3H,s); 4.92 (1H,br s); 5.41 (1H,t); 8.07 (1H,dd); 8.81 (1H,d); 9.14 (1H,d); 9.70 (1H,s).
I1		42.5-44.5	7.8(1H,m); 7.6(1H,m); 7.2-7.3(2H,m); 5.9(1H,m); 5.1-5.3(2H,m); 3.7-3.8(2H,m); 3.6(1H,m); 3.4(2H,m); 2.5(1H,m); 1.9(2H,m).
I2		115	2.4(1H,m); 2.8(1H,m); 3.3(3H,s); 3.9(2H,m); 5.4(1H,t); 7.5(2H,m); 7.9(2H,m).
I3		120	2.4(1H,m); 2.75(1H,m); 3.3(3H,s); 3.9(2H,m); 5.35(1H,t); 7.2(1H,t); 7.5(1H,m); 7.8(1H,m).

No.	Prep	mpt	nmr
I4		106	1.7(2H,s); 1.9(1H,m); 2.6(1H,m); 3.75(2H,m); 7.1(1H,t); 7.5(1H,m); 7.75(1H,m).
I5		69	2.0(1H,m); 2.5(1H,m); 2.55(3H,s); 3.5(1H,m); 3.75(2H,m); 7.1(1H,t); 7.55(1H,m); 7.75(1H,m).
I6			1.95(2H,m); 2.5(1H,m); 3.4(2H,m); 3.6(1H,m); 3.75(2H,m); 5.2(2H,m); 5.9(1H,m); 7.1(1H,t); 7.5(1H,m); 7.75(1H,m).
I7			2.36-2.50(1H,m); 2.70-2.82(1H,m); 3.32(3H,s); 3.79-4.00(2H,m); 5.34-5.40(1H,t); 7.07-7.12(1H,m); 7.40-7.46(1H,t); 7.50-7.54(1H,m); 7.66(1H,s).
I8			1.96-2.12(1H,m); 2.89-3.00(1H,m); 3.82-3.88(2H,m); 4.57-4.67(1H,m); 6.35(1H,s); 7.02-7.09(1H,m); 7.38-7.43(1H,t); 7.51-7.57(1H,m); 7.68(1H,s); 8.32(1H,s).
I9			1.99-2.14(1H,m); 2.87-2.99(1H,m); 3.83-3.91(2H,m); 4.59-4.70(1H,m); 6.48(1H,s); 7.41-7.54(2H,m); 7.82-7.87(1H,d); 7.90(1H,s); 8.32(1H,s).
I10			1.97-2.12(1H,m); 2.20-2.70(1H,s); 2.45-2.55(1H,m); 2.58(3H,s); 3.57-3.64(1H,m); 3.74-3.88(2H,m); 7.00-7.04(1H,m); 7.34-7.41(1H,t); 7.53-7.59(1H,m); 7.64(1H,s).
I11			2.33-2.48(1H,m); 2.68-2.80(1H,m); 3.32(3H,s); 3.77-3.96(2H,m); 5.32-5.38(1H,t); 7.24-7.38(2H,m); 7.54-7.59(1H,m); 7.82-7.85(1H,m).
I12			2.38-2.76(2H,m); 3.73-4.01(3H,m); 7.13-7.30(2H,m); 7.50-7.65(1H,m); 7.76-7.83(1H,m).
I13			1.90-2.04(1H,m); 2.43-2.52(1H,m); 2.51(3H,s); 3.47-3.55(1H,m); 3.70-3.84(2H,m); 7.20-7.30(2H,m); 7.60-7.65(1H,m); 7.80-7.82(1H,m).
I14			1.80-1.96(1H,m); 2.53-2.64(1H,m); 3.66-3.78(3H,m); 7.21-7.31(2H,m); 7.62-7.66(1H,m); 7.82-7.84(1H,m).

No.	Prep	mpt	nmr
I15		oil	2.36-2.48 (1H, m), 2.67-2.81 (1H, m), 3.81-3.92 (1H, m), 3.99-4.10 (1H, m), 4.56 (1H, dd), 7.42 7.51 (2H, m), 7.84-7.93 (2H, m)
I16		82-87	2.41-2.55 (1H, m), 2.68-2.84 (1H, m), 3.80-3.92 (1H, m), 4.00-4.13 (1H, m), 4.60 (1H, dd), 7.43 (1H, d), 7.50 (1H, t), 7.87 (1H, dt), 7.94 (1H, t)
I17		oil	2.41-2.55 (1H, m), 2.66-2.83 (1H, m), 3.76-3.90 (1H, m), 3.99-4.12 91H, m), 4.54-4.63 (1H, m), 7.01-7.12 (1H, m), 7.40 (1H, t), 7.56 (1H, dd), 7.66 (1H, s)
I18		oil	2.41-2.52 (1H, m), 2.67-2.81 (1H, m), 3.79-3.88 (1H, m), 4.00-4.12 (1H, m), 4.60 (1H, dd), 6.55 (1H, t), 6.94-7.00 (1H, m), 7.39 (1H, t), 7.45-7.50 (1H, m), 7.57 (1H, t)
I19		85.5-86.5	2.45 (1H, m), 2.75 (1H, m), 3.82 (1H, m), 4.16 (1H, m), 4.59 (1H, dd), 7.17 (1H, m), 7.31 (1H, t), 7.58 (1H, m), 7.70 (1H, m)
I20		oil	2.35-2.46 (1H, m), 2.55-2.70 (1H, m), 3.70-3.81 (1H, m), 3.89-4.01 (1H, m), 4.73 (1H, dd), 7.02 7.11 (1H, m), 7.40 (1H, t), 7.59 (1H, t), 7.65 (1H, s)
I21		74-75	2.05-2.20 (1H, m), 2.56-2.70 (1H, m), 3.37 (1H, s), 3.71-3.88 (2H, m), 4.45-4.55 91H, m), 7.00-7.08 (1H, m), 7.39 (1H, t), 7.57 (1H, dd), 7.64 (1H, s)
I22		78.5-80	2.03-2.19 (1H, m), 2.56-2.69 91H, m), 3.70-3.89 (2H, m), 4.49 (1H, dd), 6.54 (1H, t), 6.91-6.98 (1H, m), 7.36 (1H, t), 7.47 (1H, dd), 7,57 (1H, t)
I23		112-114	2.05-2.22 (1H, m), 2.56-2.70 (1H, m), 3.68 (1H, br s), 3.74-3.90 (2H, m), 4.52 (1H, t), 7.40-7.51 (1H, m), 7.84-7.94 (2H, m)
I24		55-56	1.97-2.11 (1H, m), 2.46-2.61 (1H, m), 3.76-3.94 (2H, m), 4.35 (1H, t), 7.44 (1H, d), 7.51 (1H, t), 7.86 (1H, d), 7.91 (1H, s)
I25		52.5-53.5	1.96-2.10 (1H, m), 2.46-2.60 (1H, m), 3.73-3.91 (2H, m), 4.34 (1H, t), 7.02-7.10 (1H, m), 7.41 (1H, t), 7.56 (1H, dd), 7.65 (1H, br s)

No.	Prep	mpt	nmr
I26		gum	1.95-2.10 (1H, m), 2.45-2.59 (1H, m), 3.72-3.90 (2H, m), 4.35 (1H, t), 6.54 (1H, t), 6.92-7.00 (1H, m), 7.37 (1H, t), 7.42-7.48 (1H, m), 7.56 (1H, t)
I27		69-70	1,69-1.93 (3H, m), 2.44-2.60 (1H, m), 2.56-2.77 (3H, m), 7.32 (1H, d), 7.41 (1H, t), 7.81 (2H, s)
I28		37-38	1.78 (2H, s), 1.81-1.97 (1H, m), 2.54-2.67 (1H, m), 3.67-3.81 (3H, m), 6.98-7.07 (1H, m), 7.39 (1H, t), 7.52-7.60 (1H, m), 7.66 (1H, s)
I29		67-69	1.78 (2H, s), 1.78-1.97 (1H, m), 2.52-2.66 (1H, m), 3.65-3.80 93H, m), 6.54 (1H, t), 6.92 (1H, dd), 7.35 (1H, t), 7.47 (1H, dd), 7.58 (1H, t)
I30		82-83	1.90 (1H, br s), 1.90-2.08 (1H, m), 2.43-2.58 (1H, m), 2.53 (3H, s), 3.53 (1H, dd), 3.75-3.90 (2H, m), 7.40 (1H, d), 7.49 (1H, t), 7.87 (1H, s), 7.92 (1H, d)
I31		60-61	1.90-2.08 (2H, m), 2.42-2.57 (1H, m), 2.53 (3H, s), 3.54 (1H, dd), 3.70-3.86 (2H, m), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.65 (1H, br s)
I32		-	1.90 (1H, br s), 1.90-2.06 (1H, m), 2.41-2.53 (1H, m), 2.53 (3H, s), 3.52 (1H, dd), 3.70-3.85 (2H, m), 6.54 (1H, t), 6.91 (1H, dd), 7.35 (1H, t), 7.43-7.49 (1H, m), 7.56 (1H, t)
I33		-	1.90-2.07 (1H, m), 2.12 (1H, s), 2.43-2.54 (1H, m), 2.54 (3H, s), 3.54 (1H, dd), 3.74-3.89 (2H, m), 7.37-7.48 (2H, m),7.83-7.94 (2H, m)
I34		-	1.19 (3H, t), 1.71 (1H, v br s), 1.90-2.06 (1H, m), 2.44-2.57 (1H, m), 2.68-2.85 (2H, m), 3.61 (1H, dd), 3.72-3.86 (2H, m), 6.98-7.05 (1H, m), 7.38 (1H, t), 7.52-7.58 (1H, m), 7.63 (1H, s)
I35		oil	1.19 (3H, t), 1.78 (1H, br s), 1.90-2.05 (1H, m), 2.43-2.56 (1H, m), 2.69-2.83 (2H, m), 3.61 (1H, dd), 3.71-3.85 (2H, m), 6.54 (1H, t), 6.92 (1H, dd), 7.35 (1H, t), 7.46 (1H, dt), 7.55 (1H, t)

No.	Prep	mpt	nmr
I36		-	0.96 (3H, t), 1.56-1.71 (2H, m), 2.01-2.22 (1H, m), 2.43-2.59 (1H, m), 2.70-3.00 (3H, m), 3.67-3.90 (3H, m), 6.97-7.06 (1H, m), 7.38 (1H, t), 7.54 (1H, dd), 7.64 (1H, s)
I37		oil	1.13 (6H, 2d), 1.87-2.09 (2H, m), 2.47-2.60 (1H, m), 3.00 (1H, hept), 3.64 (1H, dd), 3.78 (1H, dd), 7.38 (1H, d), 7.47 (1H, t), 7.85 (1H, d), 7.93 (1H, br s)
I38		-	1.92-2.08 (1H, m), 2.14 (1H, v br s), 2.45-2.58 (1H, m), 2.81-2.92 (1H, m), 2.96-3.06 (1H, m), 3.39 (3H, s), 3.43-3.60 (2H, m), 3.64 (1H, dd), 3.75-3.87 (2H, m), 7.40 (1H, d), 7.49 (1H, t), 7.77 (1H, s), 7.81 (1H, d)
I39		oil	1.90-2.08 (2H, m), 2.15 (3H, s), 2.45-2.59 (1H, m), 2.54-2.79 (2H, m), 2.85-3.08 (2H, m), 3.64 (1H, dd), 3.72-3.87 (2H, m), 6.97-7.06 (1H, m), 7.39 (1H, t), 7.50-7.60 (1H, m), 7.65 (1H, s)
I40		-	0.36-0.60 (4H, m), 2.00-2.19 (1H, m), 2.23-2.34 (1H, m), 2.41-2.56 (2H, m), 3.74 (1H, dd), 3.74 3.89 (2H, m), 7.41 (1H, d), 7.50 (1H, t), 7.87 (1H, s), 7.94 (1H, d)
I41		oil	1.90-2.08 (2H, m), 2.25 (6H, s), 2.40-2.56 (3H, m), 2.70-2.81 (1H, m), 2.85-2.96 (1H, m), 3.61 (1H, dd), 3.71-3.87 (2H, m), 6.96-7.06 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.64 (1H, s)
I42		85-86	1.90-2.08 (1H, m), 2.26 (2H, v br s), 2.47-2.61 (1H, m), 2.82-3.05 (2H, m), 3.56-3.84 (5H, m), 7.02 (1H, dd), 7.39 (1H, t), 7.55 (1H, dd), 7.65 (1H, s)
I43		oil	1.86-2.07 (1H, m), 2.26 (1H, t), 2.57-2.60 (1H, m), 3.47 (1H, dd), 3.71 (1H, dd), 3.75-3.91 (3H, m), 6.98-7.07 (1H, m), 7.39 (1H, t), 7.57 (1H, dd), 7.64 (1H, s)
I44		oil	1.82-2.06 (2H, m), 2.44-2.58 (1H, m), 3.31-3.48 (2H, m), 3.65 (1H, dd), 3.75-3.89 (2H, m), 5.15 (1H, dt), 5.26 (1H, dt), 5.85-6.01 (1H, m), 7.41 (1H, d), 7.50 (1H, t), 7.86 (1H, s), 7.92 (1H, d)

No.	Prep	mpt	nmr
I45		oil	1.86-2.07 (1H, m), 2.42-2.57 (1H, m), 3.31-3.47 (2H, m), 3.64 (1H, dd), 3.71-3.86 (2H, m), 5.15 (1H, dd), 5.26 (1H, dd), 5.93-6.01 (1H, m), 6.98-7.07 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.64 (1H, s)
I46		oil	1.84 (1H, v br s), 1.90-2.06 (1H, m), 2.44-2.58 (1H, m), 1.81 (1H, dd), 1.95 (1H, dd), 3.42 (6H, 2s), 3.64 (1H, dd), 3.73-3.85 (1H, m), 4.51 (1H, t), 6.98-7.06 (1H, m), 7.38 (1H, t), 7.56 (1H, dd), 7.63-7.66 (1H, m)
I47		93-94	2.00-2.16 (1H, m), 2.85-2.98 (1H, m), 3.85-4.00 (2H, m), 4.12-4.23 (1H, m), 4.56 (1H, s), 6.73 (2H, d), 6.81 (1H, t), 7.19-7.28 (2H, m), 7.45 (1H, d), 7.54 (1H, t), 7.90-8.00 (2H, m)
I48		-	1.91-2.06 (1H, m), 2.14 (1H, v br s), 2.38-2.50 (1H, m), 3.63 (1H, dd), 3.70-3.86 (2H, m), 3.91 (1H, d), 3.98 (1H, d) 7.20-7.43 (6H, m), 7.47 (1H, t), 7.82-7.95 (2H, m)
I49		oil	1.91-2.07 (1H, m), 2.28 (1H, v br s), 2.50-2.64 (1H, m), 3.23-3.57 (2H, m), 3.66-3.85 (3H, m), 6.99-7.09 (1H, m), 7.40 (1H, t), 7.55 (1H, dd), 7.64 (1H, s)
I50		81-82	2.28-2.58 (2H, m), 3.60 (3H, s), 3.76-3.93 (3H, m), 8.44 (1H, s), 7.41 (1H, d), 7.50 (1H, t), 7.86-7.98 (2H, m)
I51		79-80.5	1.30 (3H, t), 1.41-1.59 (1H, m), 3.55-3.90 (4H, m), 4.22 (2H, q), 7.41 (1H, d), 7.49 (1H, t), 7.84-7.95 (2H, m)
I52		71-72	1.89-2.07 (1H, m), 2.41 (1H, br s), 2.44-2.57 (1H, m), 3.60-3.87 (8H, m), 6.99-7.07 (1H, m), 7.38 (1H, t), 7.55 (1H, dd), 7.64 (1H, s)
I53		81-82.5	1.45 (9H, m), 1.90-2.08 (1H, m), 2.43-2.56 (1H, m), 3.47 (1H, d), 3.55 (1H, d), 3.63 (1H, dd), 3.70-3.86 (2H, m), 6.98-7.05 (1H, m), 7.39 (1H, t), 7.50-7.58 (1H, m), 7.65 (1H, s)
I54		100-103	1.18 (9H, s), 1.92-2.08 (1H, m), 3.54 (1H, t), 3.68-4.00 (4H, m), 6.97-7.05 (1H, m), 7.38 (1H, t), 7.50-7.58 (1H, m), 7.64 (1H, s)

No.	Prep	mpt	nmr
I55		65-66.5	1.90-2.05 (1H, m), 2.28 (1H, v br s), 2.53-2.66 (1H, m), 3.61-4.01 (5H, m), 7.00-7.08 (1H, m), 7.41 (1H, t), 7.54 (1H, dd), 7.65 (1H, s)
I56		-	2.22 (1H, m), 2.42 (3H, s), 2.77 (1H, m), 3.91 (2H, m), 4.41 (1H, t), 7.4-7.55 (2H, m), 7.89 (2H, m)
I57		-	2.20 (1H, m), 2.42 (3H, s), 2.76 (1H, m), 3.89 (2H, m), 4.43 (1H, t), 7.04 (1H, d), 7.40 (1H, t), 7.56 (1H, d), 7.62 (1H, s)
I58		gum	2.10-2.28 (1H, m), 2.42 (3H, s), 2.66-2.81 (1H, m), 3.84-3.93 (2H, 2d), 4.43 (1H, t), 6.14 (1H, t), 6.90-6.97 (1H, m), 7.36 (1H, t), 7.44 (1H, dd), 7.56 (1H, t)
I59		103-106	
I60		142-144	
I61		95-97	
I62		109-112	
I63		136-138	
I64		95-97	
I65		142-150	
I66		81-82	1.35(9H,s); 2.4(2H,m); 3.25(2H,t); 5.05(1H,br s); 5.25(1H,dd); 7.25(1H,t); 7.35(1H,t); 7.5(1H,s); 9.0(1H,br s).
I67		67-69	1.35 (9H, s), 2.5 (2H, m), 3.2 (2H, t), 3.9 (3H, s), 5.0 (1H, br s), 5.35 (1H, dd), 8.15 (1H, s), 10.1 (1H, br s)
I68		67-69	1.35 (9H, s), 2.5 (2H, m), 3.2 (2H, t), 5.0 (1H, br s), 5.35 (1H, dd), 7.8 (1H, s), 10.0 (1H, br s)
I69		oil	3.00 (2H, m), 4.80(1H, m) 5.47 (2H, s); 6.55 (1H, t); 6.99 (1H, dd); 7.28(1H, m);7.39 (1H, t); 7.47 (1H, t); 10.35 (1H, s)
I70		oil	0.96(3H, t); 1.59 (2H, sextet); 1.91(1H, br m); 2.70 (1H, m); 2.80 (1H, m) 4.80 (2H, s); 5.15 (1H, s); 7.49 (2H, m); 7.74 (2H, m)

No.	Prep	mpt	nmr
I72		62.6-63.6	1.20 (3H, t); 1.79(1H, s); 2.84 (2H, m); 4.80 (2H, m); 5.18 (1H, s) 7.55 (2H, m); 7.74 (2H, m)
I73			2.10 (1H, br s); 3.42 (2H, dt); 4.79 (2H, m); 5.13 (1H, m) 5.15 (1H, s); 5.28 (1H, m); 5.90 (1H, m); 7.49 (2H, m); 7.69 (1H, m); 7.77 (1H, s)

Biological Data

The herbicidal activity of the compounds was tested as follows. Each chemical was formulated in one of two ways. Either the chemical was dissolved in an appropriate amount of water, dependent on the amount of solvent/surfactant blend required such that the total volume is $5cm^3$. Then a solvent sufficient blend comprised 78.2 g/litre of Tween 20 and 21.8 g/litre of Span 80 adjusted to 1 litre using methylcyclohexanone was added to the solution. Alternatively, the chemical was dissolved in water to the required concentration and 0.1% Tween added. Tween 20 is a Trade Mark for a surface-active agent comprising a condensate of 20 molar proportions of ethylene oxide with sorbitan laurate. Span 80 is a Trade Mark for a surface-active agent comprising sorbitan mono-laurate. If the chemical did not dissolve, the volume was made up to $5cm^3$ with water, glass beads were added and this mixture was then shaken to effect dissolution or suspension of the chemical, after which the beads were removed. In all cases, the mixture was then diluted to the required spray volume. If sprayed independently, volumes of $25cm^3$ and $30cm^3$ were required for post-emergence tests; if sprayed together, $45cm^3$ was required. The sprayed aqueous emulsion contained 4% of the initial solvent/surfactant mix and the test chemical at an appropriate concentration.

The spray compositions so prepared were sprayed on to young pot plants (post-emergence test) at a spray volume equivalent to 1000 litres per hectare. Damage to plants was assessed 13 days after spraying by comparison with untreated plants, on a scale of 0 to 9 where 0 is 0% damage, 1 is 1-5% damage, 2 is 6-15% damage, 3 is 16-25% damage, 4 is 26-35% damage, 5 is 36-59% damage, 6 is 60-69% damage, 7 is 70-79% damage, 8 is 80-89% damage and 9 is 90-100% damage.

In a test carried out to detect pre-emergence herbicidal activity, crop seeds were sown at 2 cm depth and weed seeds at 1 cm depth beneath compost and sprayed with the compositions at the rate of 1000 litres per hectare. 20 days after spraying, the seedlings in the sprayed plastic trays were compared with the seedlings in unsprayed control trays, the damage being assessed on the same scale of 0 to 9.

The results of the pre-emergence tests are given in Table IV below.

TABLE IV

Comp. No.	Pre or Post	DA	Rate g/ha	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	EH	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
1	PREM	20	1000	5	6	0	0	4	0	0	8	9	0	6	0		0	0	0	0	0	5	2	7	0	0	5	0
1	PREM	20	1000			6	6	2				9		9			6	7					3	9	9	9	7	5
2	PREM	20	1000	3	5	0	0	0	0	0	0	5	0	0	0		2	0	-	3	0	0	5	3	0	4	0	0
4	PREM	20	1000	0		0	0	0				0		0			0	0					0	0	-	0	0	0
5	PREM	20	250			0	0	0				3		5			0	0					0	0	3	5	2	0
6	PREM	20	500			0	1	0				9		9			2	3					5	9	5	9	9	2
6	PREM	20	500			1	2	0				9		9			0	0					9	9	9	7	9	3
7	PREM	20	500			0	0	3				2		3			0	0					0	0	3	0	0	2
8	PREM	20	500			0	9	5				9		9			0	0					3	9	8	9	9	0
9	PREM	20	500			0	0	0				0		0			0	0					3	0	0	0	0	0
10	POST	13	500	5	5	4	2	2	0	3	4	5	3	5		5	5	3	3	4	0	0	0	0	0	0	0	0
11	PREM	20	500			2	3	0				0		0			0	0					0	0	4	0	0	0
12	PREM	20	500			0	0	0				2		0			0	0					0	0	0	0	0	0
15	PREM	20	500			0	2	5				0		0			0	0					0	0	0	0	0	0
16	PREM	20	250			0	0	2				9		9			3	3					6	7	2	9	5	2
17	PREM	19	500			2	4	2				9		9			3	5					5	9	9	9	9	3
18	PREM	19	500			5	0	2				9		9			2	9					3	9	9	9	9	3
19	PREM	19	250			5	9	0				9		9			5	2					7	9	8	9	9	5
20	PREM	19	250			2	0	2				9		9			2	2					2	5	7	2	4	2
21	PREM	20	500			3	8	0				9		9			8	5					5	9	9	9	9	8
21	PREM	20	500	9	6	4	6	8	5	9	9	9	5	9		9	8	8	5	6	6	9	7	9	9	9	9	9
22	PREM	20	500			0	0	0				0		0			0	0					0	0	2	0	0	0
23	PREM	20	500			0	0	0				0		0			2	0					0	0	0	0	5	0
24	PREM	20	500			0	0	0				7		3			0	0					0	0	2	3	0	0
25	PREM	20	500			0	0	2				0		0			0	0					0	0	0	0	0	0
26	PREM	20	500			0	0	2				0		0			0	0					0	0	0	0	0	0
27	PREM	20	500			0	0	0				0		0			0	0					0	0	0	0	0	0
28	PREM	20	500			0	0	0				9		9			4	3					2	9	9	9	9	0

Comp. No.	Pre or Post	DA	Rate g/ha	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	EH	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
29	PREM	20	500			2	2	0				9		9			3	3					9	9	9	9	9	6
30	PREM	20	500			0	0	0				0		0			0	0					0	0	0	0	0	0
31	PREM	20	500			0	0	0				0		9			0	0					0	3	0	2	9	3
32	PREM	20	500			2	5	0				0		9			4	5					9	9	0	9	9	5
34	PREM	20	500			5	9	0				0		9			8	9					2	9	2	9	9	8
35	PREM	20	500			2	4	0				0		9			3	6					6	9	6	9	9	9
36	PREM	20	500			6	5	4				0		9			7	9					1	9	0	9	9	9
36	PREM	20	500			8	9	0				0		9			9	9					6	9	0	9	9	9
36	PREM	20	500			7	7	0				0		9			9	9					0	9	0	9	9	9
36	PREM	20	500			5	9	0				0		9			7	9					2	9	0	9	9	9
37	PREM	20	250			0	0	0				0		0			0	0					0	0	0	0	0	0
38	PREM	20	250			0	0	0				0		0			0	0					0	0	0	0	0	0
39	PREM	20	250			0	0	0				0		0			0	0					3	9	0	9	9	9
40	PREM	20	250			3	0	0				0		0			0	0					9	9	0	9	9	9
41	PREM	20	500			2	9	0				9		9			5	6					1	9	0	9	9	9
42	PREM	20	500			0	8	0				9		9			4	5					6	9	0	9	9	9
43	PREM	20	500			2	0	4				9		9			3	4					0	9	0	9	9	9
44	PREM	20	500			3	3	2				9		9			2	9					2	9	0	9	9	9
45	PREM	20	500			0	0	0				9		9			2	9					0	9	0	9	9	9
47	PREM	20	250			0	5	0				9		0			0	5					2	9	0	9	9	9
48	PREM	20	250			0	0	0				5		3			2	0					0	9	0	9	9	9
49	PREM	20	250			0	6	2				9		9			0	3					4	9	0	9	9	9
50	PREM	20	250			0	7	0				9		9			9	4					9	9	0	9	9	9
51	PREM	20	500			7	9	0				9		9			4	9					7	9	0	9	9	9
52	PREM	20	500			3	7	0				9		9			7	9					8	9	0	9	9	9
53	PREM	20	500			4	9	0				9		9			8	6					2	9	0	9	9	9
54	PREM	20	500			5	9	8				9		9			0	5					9	9	3	9	9	9
55	PREM	20	500			0	3	-				9		9			9	9					0	7	9	9	5	9
56	PREM	20	500			8	9	3				9		9			0	6					9	9	9	9	9	7
57	PREM	20	500			0	0	0				9		9			5	6					0	9	9	9	9	0

Comp. No.	Pre or Post	DA	Rate g/ha	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	EH	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
58	PREM	20	500			0	8	2				9		9			2	0					7	9	9	9	9	6
59	PREM	20	500			0	8	0				9		9			0	4					9	9	9	9	9	7
60	PREM	20	500			0	0	0				9		9			2	0					3	5	7	9	7	0
61	PREM	20	500			0	0	0				9		9			0	0					6	9	4	7	8	0
63	PREM	20	500			7	9	0				9		9			8	7					9	9	9	9	9	8
64	PREM	20	500			2	9	0				9		9			6	7					9	9	9	9	9	8
65	PREM	20	500			0	5	0				9		9			4	9					5	9	8	9	9	5
67	PREM	20	500			0	0	0				0		0			0	0					0	0	0	0	0	0
68	PREM	20	500			0	3	0				9		8			0	0					0	0	2	7	0	0
69	PREM	20	500			1	6	0				9		9			1	2					6	9	8	9	8	3
70	PREM	20	500			5	9	4				9		9			6	7					8	9	9	9	9	2
71	PREM	20	500			0	9	0				9		9			2	5					3	7	9	9	9	0
72	PREM	20	500			6	9	2				9		9			9	6					9	9	9	9	9	5
73	PREM	20	500			2	7	0				9		9			0	3					9	9	9	9	9	6
74	PREM	20	500			7	7	2				9		9			9	9					8	9	9	9	9	3
74	PREM	20	500			8	8					9		9			9	9					7	9	9	9	9	5
75	PREM	20	500			0	7	0				9		9			2	2					5	9	6	9	9	2
76	PREM	20	500			0	7	0				9		9			2	5					6	9	9	9	9	0
77	PREM	20	500			0	2					0		2			0	0					0	0	0	0	2	0
78	PREM	20	500			4	9					9		9			6	8					9	9	9	9	9	9
79	PREM	20	500			0	5					9		9			2	5					9	9	9	9	9	0
80	PREM	20	500			0	5					9		9			0	5					9	9	9	9	9	0
81	PREM	20	500			0	5					9		9			0	0					6	9	9	9	9	0
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83	PREM	20	500			0	3	8				0		0			0	0					0	0	0	0	0	0
84	PREM	20	500			5	6	0				9		9			3	5					7	9	9	9	9	4
85	PREM	20	500			0	5	0				9		9			0	0					3	6	3	5	5	2
86	PREM	20	500			4	9	0				9		9			5	9					8	9	9	9	9	2
87	PREM	20	500			0	5	0				9		9			0	0					4	8	0	9	8	2
88	PREM	20	500			8	9					9		9			9	9					9	9	9	9	9	8

Comp. No.	Pre or Post	DA	Rate g/ha	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	EH	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
89	PREM	20	500			0	5					9		9			0	0					5	9	9	8	9	2
90	PREM	20	500			0	7					9		9			3	3					9	9	9	9	9	5
91	PREM	20	500			5	9					9		9			5	6					9	9	9	9	9	6
92	PREM	20	500			0	0					0		0			0	0					0	0	0	0	0	0
93	PREM	20	500			6	8					9		9			5	9					9	9	9	9	9	5
94	PREM	20	500			3	0					9		9			9	9					9	9	9	9	9	3
95	PREM	20	500			5	9					9		9			9	9					6	9	9	9	9	6
96	PREM	20	500			3	5					9		9			3	2					9	9	9	9	9	4
97	PREM	20	500			2	6					9		9			2	2					9	9	9	9	9	5
98	PREM	20	500			5	0					9		9			2	3					9	9	9	9	9	2
99	PREM	20	500			5	4					9		9			3	3					8	5	9	9	9	2
100	PREM	20	500			3	9					9		9			5	9					9	9	9	9	9	2
101	PREM	20	500			0	0					9		9			0	0					2	0	8	7	0	0
102	PREM	20	500			0	8					9		9			0	3					9	9	9	9	9	0
103	PREM	20	500			0	7					9		9			0	0					9	9	9	9	9	2
104	PREM	20	500			0	0					9		9			0	0					0	4	5	8	7	0
105	PREM	20	500			0	8					9		9			0	0					9	9	9	9	7	0
106	PREM	20	500			2	9					9		9			6	3					9	9	9	9	9	2
107	PREM	20	500			2	6					9		9			0	0					7	7	9	9	9	3
108	PREM	20	500			7	8					9		9			0	2					9	9	9	9	9	5
109	PREM	20	500			0	0					9		9			0	0					0	0	9	8	4	0
110	PREM	20	500			0	8					9		9			0	0					9	9	9	9	9	0
111	PREM	20	500			0	9					9		9			0	2					9	9	9	9	9	4
112	PREM	20	250			0	5					9		9			0	0					7	9	7	9	9	0
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118	PREM	20	500			0	8					9		9			0	2					9	9	9	9	9	0

Comp. No.	Pre or Post	DA	Rate g/ha	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	EH	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
123	PREM	20	500			0	9					9		9			2	6					9	9	9	9	9	6
124	PREM	20	500			8	4					9		9			9	9					8	9	9	9	9	5
125	PREM	20	500			5	9					9		9			9	7					9	9	9	9	9	5
126	PREM	20	500			0	7					9		8			0	0					0	0	0	0	0	0
127	PREM	20	500			0	0					9		9			0	0					0	0	5	7	6	0
128	PREM	20	500			9	9					9		9			7	7					9	9	9	9	8	2
129	PREM	20	250			2	5					9		9			2	2					2	7	8	9	6	2
130	PREM	20	500			0	3					9		9			0	2					0	5	4	7	5	0
131	PREM	20	500			0	0					3		2			0	0					0	0	0	0	0	0
132	PREM	20	250			0	0					9		9			0	0					0	2	0	7	0	0
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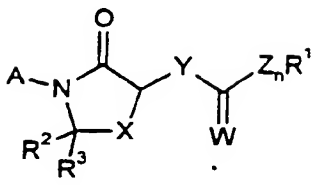
142	PREM	20	250			0	0	0				7		0			0	0					0	4	2	3	0	0
144	PREM	20	250	0		0	0	0				9		9			0	0					9	9		9	9	0
145	PREM	20	250			0	0											0					8	9		9	9	0
146	PREM	20	250			0	0	0										0					9	9		9	8	0
147	PREM	20	250			0	0											0					6	9		9	9	2
150	PREM	20	500			0	0	0				9		9			3	2					9	9			9	

TABLE V

Abbreviations used for Test Plants in Table IV

BV - Sugar beet
GM - Soybean
ZM - Maize
OS - Rice
PA - Polygonum aviculare
CA - Chenopodium album
GA - Galium aparine
AR - Amaranthus retroflexus
MI - Matricaria inodora
BP - Bidens pilosa
EH - Euphorbia heterophylla
IH - Ipomoea hederacea
AT - Abutilon theophrasti
XT - Xanthium strumarium
AF - Avena fatua
AM - Alopecurus myosuroides
LR - Lolium rigidum
SH - Sorghum halepense
SV - Setaria viridis
PD - Panicum dichotomiflorum
EC - Echinochloa crus-galli
CE - Cyperus esculentus

STRUCTURES



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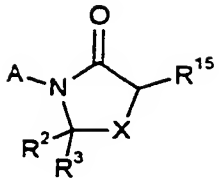

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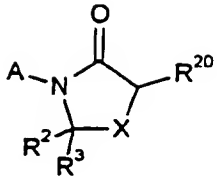

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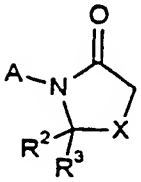

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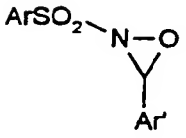

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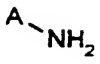

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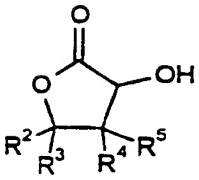

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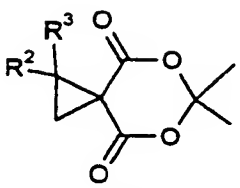

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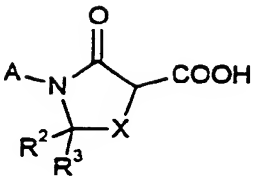

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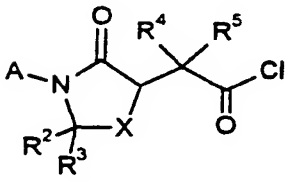

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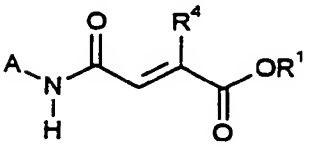

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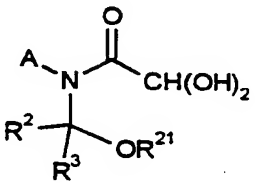

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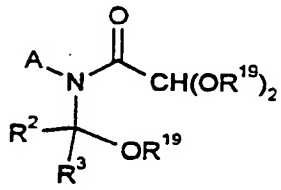

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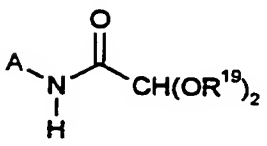

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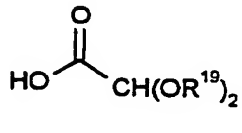

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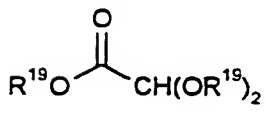

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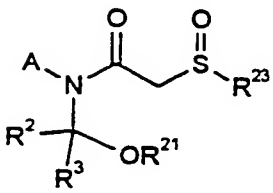

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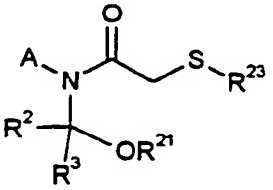

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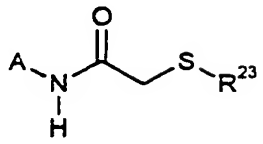
STRUCTURES



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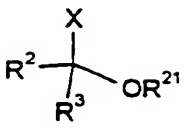

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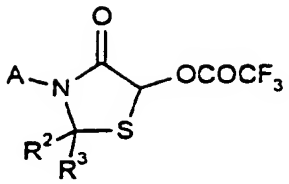

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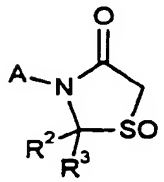

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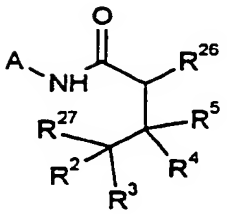

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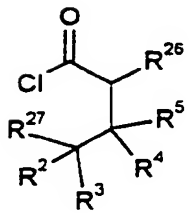

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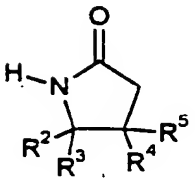

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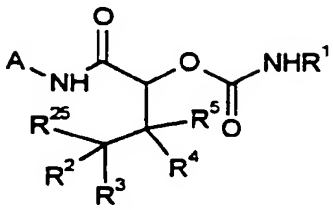

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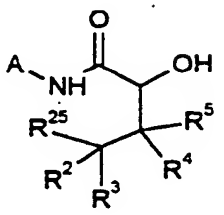

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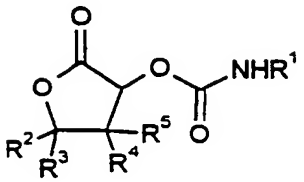

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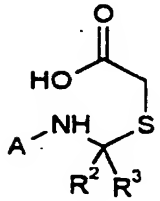

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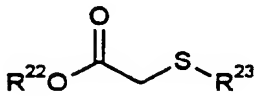

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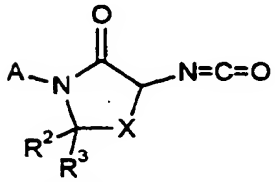

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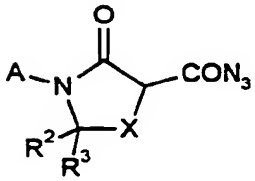

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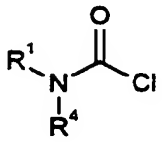

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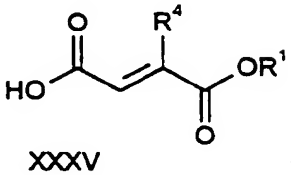

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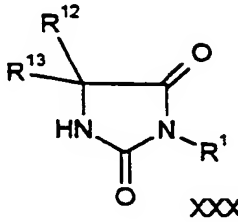
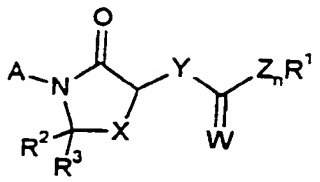


XXXVI

CLAIMS

1. A compound of general formula I:



I

wherein

X is O, S or CR^4R^5;

Z is O, S or NR^4;

n is 0 or 1;

Y is O, S, NR^6 or CR^4R^5;

each R^4 and R^5 is, independently, hydrogen or C_1-C_4 alkyl;

R^6 is H, OH, CHO, $NR^{16}R^{17}$ or C_1-C_{10} hydrocarbyl, O-(C_1-C_{10} hydrocarbyl), either of which may be substituted with one or more substituents chosen from OR^{16}, COR^{16}, $COOR^{16}$, $OCOR^{16}$, CN, halogen, $S(O)_pR^{16}$, $NR^{16}R^{17}$, NO_2, $NR^{16}COR^{17}$, $NR^{16}CONR^{17}R^{18}$, $CONR^{16}R^{17}$ or heterocyclyl;

R^{16}, R^{17} and R^{18} are each, independently, hydrogen, C_1-C_6 hydrocarbyl or C_1-C_6 halohydrocarbyl;

p is 0, 1 or 2;

alternatively:

when Y is NR^6 or CR^4R^5, and:

a) Z is NR^4; or

b) n is 0;

the substituents of Y and Z or Y and R^1 may together form a bridge represented by the formula $-Q^1-Q^2-$ or $-Q^1-Q^2-Q^3-$, where Q^1, Q^2 and Q^3 each independently represent $CR^{12}R^{13}$, $=CR^{12}$, CO, NR^{14}, =N, O or S;

each of R^{12} and R^{13} independently represents hydrogen, C_1-C_4 alkyl, OH or halogen;

R^{14} represents hydrogen or C_1-C_4 alkyl;

W is O or S;

R^1 is hydrogen or C_1-C_{10} hydrocarbyl or heterocyclyl having 3 to 8 ring

atoms, either of which may optionally be substituted with one or more substituents chosen from halogen (i.e. chlorine, bromine, fluorine or iodine), hydroxy, $SO_2NR^aR^b$ (where R^a and R^b are independently H or C_{1-6} alkyl), SiR^c_3 (where each R^c is independently C_1-C_4 alkyl or phenyl), cyano, nitro, amino, mono- and dialkylamino in which the alkyl groups have from 1 to 6 or more carbon atoms, acylamino, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, carboxy, carboxyamide, in which the groups attached to the N atom may be hydrogen or optionally substituted lower hydrocarbyl; alkoxy carbonyl wherein the alkoxy group may have from 1 to 6 or more carbon atoms, or aryl such as phenyl;

R^2 and R^3 are each independently hydrogen or C_1-C_4 alkyl;

A is an aromatic or heteroaromatic ring system optionally substituted with one or more substituents selected from: halogen or C_1-C_{10} hydrocarbyl, -O(C_1-C_{10} hydrocarbyl), -S(C_1-C_{10} hydrocarbyl), -SO(C_1-C_{10} hydrocarbyl) or -SO_2(C_1-C_{10} hydrocarbyl), cyano, nitro, SCN, SiR^c_3 (where each R^c is independently C_1-C_4 alkyl or phenyl), COR^7, CR^7NOR^8, NHOH, ONR^7R^8, SF_5, $COOR^7$, $SO_2NR^7R^8$, OR^9 or $NR^{10}R^{11}$; and in which any ring nitrogen atom may be quaternised or oxidised; alternatively, two or more substituents of the group A may combine to form a fused 5- or 6-membered saturated or partially saturated carbocyclic or heterocyclic ring in which any carbon or quaternised nitrogen atom may be substituted with any of the groups mentioned above for A or in which a ring carbon atom may be part of a carbonyl group or a nitrogen atom may be oxidised;

R^7 and R^8 are each independently hydrogen or C_1-C_{10} hydrocarbyl;

R^9 is hydrogen, C_1-C_{10} hydrocarbyl, SO_2(C_1-C_{10} hydrocarbyl), CHO, CO(C_1-C_{10} hydrocarbyl), COO(C_1-C_{10} hydrocarbyl) or $CONR^7R^8$;

R^{10} and R^{11} are each independently hydrogen, C_1-C_{10} hydrocarbyl, O(C_1-C_{10} hydrocarbyl), SO_2(C_1-C_{10} hydrocarbyl), CHO, CO(C_1-C_{10} hydrocarbyl), COO(C_1-C_{10} hydrocarbyl) or $CONR^7R^8$;

any of the hydrocarbyl groups within the group A may optionally be substituted with halogen (i.e. chlorine, bromine, fluorine or iodine), hydroxy, $SO_2NR^aR^b$ (where R^a and R^b are independently H or C_{1-6} alkyl), cyano, nitro, amino, mono- and dialkylamino in which the alkyl groups have from 1 to 6 or more carbon atoms, acylamino, C_{1-6} alkoxy, C_{1-6} haloalkoxy,

C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, carboxy, carboxyamide, in which the groups attached to the N atom may be hydrogen or lower hydrocarbyl optionally substituted with halogen; alkoxy carbonyl wherein the alkoxy group may have from 1 to 6 or more carbon atoms, or aryl such as phenyl;

provided that:

i) when A is a phenyl group or a substituted phenyl group in which no two adjacent substituents are joined to form a partially or fully saturated ring and Y is O; then Z is not NR^4;

ii) when X is S, R^2 and R^3 are both H and Y is CH_2; then the group $(Z)_n$-R^1 is other than OH, OC_{1-4} alkyl, $NHN(C_{1-2}$ alkyl$)_2$;

iii) when X is CH_2, R^2 and R^3 are both H, Y is NH or NCH_3, A is unsubstituted phenyl or phenyl substituted with halo, methoxy, CF_3 or NO_2 and n is 0; then R^1 is other than pyridyl, trimethoxyphenyl or dihalophenyl.

2. A compound as claimed in claim 1 wherein the group A is substituted with one or more substituents chosen from C_1-C_4 alkyl, C_1-C_4 haloalkyl, O(C_1-C_4 alkyl), O(C_1-C_4 haloalkyl), S(C_1-C_4 alkyl), S(C_1-C_4 haloalkyl) and halo.

3. A compound as claimed in claim 2 wherein A is substituted with one or more substituents chosen from trifluoromethyl, trichloromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, dichloromethoxy, fluoromethoxy, chloromethoxy, trichloroethoxy, trifluoroethoxy, dichloroethoxy, difluoroethoxy, fluoroethyoxy, trifluoromethylthio, ethoxy, methoxy, fluoro, chloro, bromo, iodo and methyl.

4. A compound as claimed in any one of claims 1 to 3, wherein R^1 is optionally substituted C_1-C_6 alkyl, for example methyl, $-C(CH_3)_3$, $-CH(CH_3)_2CN$, $-CH_2C(CH_3)_3$, $-CH_2CH_3$, $C(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $CH_2C(CH_3)_2$ or $C(CH_3)_2Cl$; C_2-C_6 alkenyl, for example $C(CH_3)_2CH{=}CH_2$ and $CH_2C(CH_3)_2CH{=}CH_2$; alkynyl, for example $CH_2C{\equiv}CH$ or $C(CH_3)_2C{\equiv}CH$; C_1-C_6 alkyl-OH, for example $C(CH_3)_2CH_2OH$; optionally substituted C_3-C_8 cycloalkyl, for example cyclobutyl, 1-methylcyclobutyl, 1-methylcyclopropyl, 1-methylcyclopentyl,

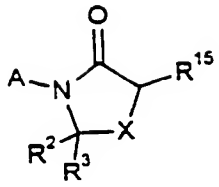
1-methylcyclohexyl, 1-cyanocyclopropyl, 1-cyanocyclobutyl, 1-cyanocyclopentyl, 1-cyanocyclohexyl, 1-acetylenylcyclopropyl, 1-acetylenylcyclobutyl, 1-acetylenylcyclopentyl, 1-acetylenylcyclohexyl; optionally substituted benzyl, optionally substituted phenyl; optionally substituted heterocyclyl, for example pyrrolyl, methylisoxazolyl or methylpyridyl; COC_1-C_6 alkyl, for example $COC(CH_3)_3$; C_1-C_6 alkyl$COO(C_1$-C_4 alkyl), for example $C(CH_3)_2COOC_2H_5$; or SiR^c_3, for example trimethylsilyl.

5. A compound as claimed in any one of claims 1 to 4, wherein, independently or in any combination:
X is S, O or CH_2
Y is S, O, CH_2, $CH(CH_3)$ or NR^6;
Z is NH or O; or n is O and Z is not present;
R^2 and R^3 are both hydrogen; or
Q^1, Q^2 and Q^3, when present are CH_2 or C=O.

6. A compound as claimed in claim 5, wherein Y is a group NR^6 and R^6 is hydrogen, -CHO, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, for example benzyl which is optionally substituted with C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy, (C_1-C_6 alkyl)aryl, (C_1-C_6 alkyl)heterocyclyl, -O(C_1-C_6 alkyl), -O(C_1-C_6 alkyl)aryl, -O(C_1-C_6 alkyl)heterocyclyl, -C_1-C_6 alkyl-OH, -(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-S-(C_1-C_6 alkyl), -C_1-C_6 alkyl(OC_1-C_6 alkyl)$_2$, -C_1-C_6 alkyl-NH(C_1-C_6 alkyl), -C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl-$COO(C_1$-C_6 alkyl), -C_1-C_6 alkyl-$OCONH(C_1$-C_6 alkyl) and -C_1-C_6 alkyl-$OCO(C_1$-C_6 alkyl).

7. Any one of the compounds of Table I.

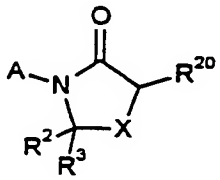
8. A process for the preparation of a compound as claimed in any one of claims 1 to 7, the process comprising:
a. reacting a compound of general formula II:



II

wherein A, R^2, R^3 and X are as defined for general formula I and R^{15} is OH, SH or NHR^6, wherein R^6 is as defined for general formula I; with a compound of formula of general formula R^1COCl, R^1OCOCl, R^1-N=C=O, R^1-N=C=S or R^1R^4NOCl; or

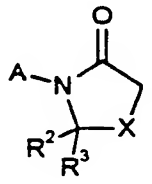
b. reacting a compound of general formula III:



III

wherein A, R^2, R^3 and X are as defined for general formula I and R^{20} is Cl, Br, methane sulfonyloxy or toluene sulfonyloxy; with a compound of general formula $HSCOR^1$; or

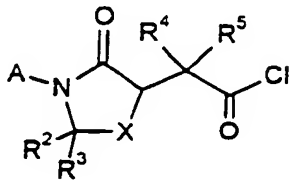
c. reacting the anion of compound of general formula IV:



IV

wherein A, R^2, R^3 and X are as defined in general formula I; with a compound of general formula $BrCH_2COOR^1$; or

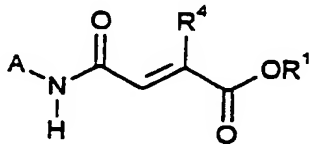
d. reacting a compound of general formula X:



X

wherein A, X, R^2, R^3, R^4 and R^5 are as defined in general formula I; with a compound of general formula NR^1R^4; or

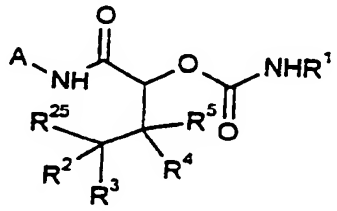
e. reacting a compound of general formula XI:



XI

wherein R^1 and A are as defined for general formula I; with a compound of general formula $R^2R^3C=O$ in the presence of a strong base; or

f. cyclising a compound of general formula XXVII:



XXVII

wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined for general formula I and R^{25} is halogen such as chloro or bromo under basic conditions; or

g. treating a compound of general formula I, in which Z is NH and Y is $N\text{-}Q^1\text{-}C(=O)\text{-}L$ in which L is a leaving group such as methoxy, ethoxy, chloro or bromo and Q^1 is as defined above, with a strong base such as

sodium hydride to give a compound of general formula I in which Z is NR^4 and Y is NR^6 and R^4 and R^6 form a bridge of formula $-Q^1-C(=O)-$; or

h. reacting a compound of general formula I in which both Y and Z are NH with a compound of formula $LC(=O)-C(=O)LC$ or $LC(=O)-Q^2-C(=O)LC$ in which Q^2 and L are as defined above to give a compound of general formula I in which Z is NR^4 and Y is NR^6 and R^4 and R^6 form a bridge of formula $-C(=O)-C(=O)-$ or $-C(=O)-Q^2-C-(=O)-$; or

i. treating a compound of general formula I in which Z is NH and Y is NCH_2CHL_2, wherein L is a leaving group as defined above with an aqueous inorganic acid such as hydrochloric acid to give a compound of general formula I in which Z is NR^4 and Y is NR^6 and R^4 and R^6 form a bridge of formula $-C=C-$; or

j. reacting a compound of general formula I in which both Y and Z are NH with CHO-CHO to give a compound of general formula I in which Z is NR^4 and Y is NR^6 and R^4 and R^6 form a bridge of formula $-C(=O)-C-$; or

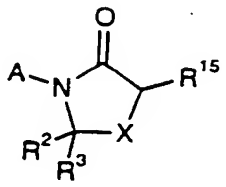
k. reacting a compound of general formula I in which both Y and Z are NH with paraformaldehyde to give a compound of general formula I in which Z is NR^4 and Y is NR^6 and R^4 and R^6 form a bridge of formula $-CH_2-OCH_2-$.

9. A compound of any one of general formulae II, III, IV, X, XI or XXVII as defined above.

10. A herbicidal composition comprising a compound as claimed in any one of claims 1 to 7 or a compound of general formula XXV in combination with an agriculturally acceptable carrier or diluent.

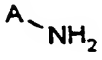
11. A process of severely damaging or killing unwanted plants, which comprises applying to the plants, or to the growth medium of the plants, a herbicidally effective amount of a compound as claimed in any one of claims 1 to 7 or a compound of general formula XXV.

12. A process for the preparation of a compound of general formula II:



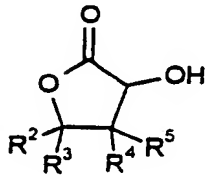
II

wherein A, R^2, and R^3 are as defined for general formula I, X is CH_2 and R^{15} is OH, the process comprising reacting an aniline derivative of general formula VI:



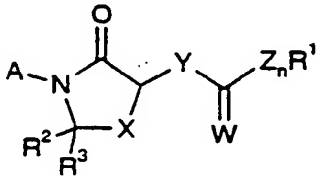
VI

wherein A is as defined for general formula I; with a compound of general formula VII:



VII

wherein R^2 and R^3 are as defined for general formula I.



I

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 95/01224

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/26 A01N43/08 C07D277/14 C07D277/16 C07D277/18
A01N43/78 C07D263/18 C07C233/09 C07C271/10 C07D405/14
C07D417/04 C07D413/04 C07D403/04 C07D409/04 C07D263/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 200 415 (UNIROYAL CHEMICAL COMPANY) 10 December 1986 cited in the application see claims	1-7,9
X	FR,A,2 102 279 (TANNABE SEIYAKU CO.,LTD) 7 April 1972 see claims	1-7,10
X	WO,A,93 24483 (CIBA-GEIGY AG) 9 December 1993 see claims	1-7,10
X	EP,A,0 378 791 (NIHON TOKUSHU NOYAKU SEIZO K.K.) 25 July 1990 see claims	1,9-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1995	31. 08. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/GB 95/01224

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 956 006 (FRANK X. WOOLARD) 11 September 1990 see claims	1,9-11
X	EP,A,0 339 390 (NIHON TOKUSHU NOYAKU SEIZO K.K.) 2 November 1989 see claims	1,9-11
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 26, no. 3, March 1961 EASTON US, pages 697-700, PAUL G. CAMPBELL ET AL 'Some new fumaric acid derivatives.Preparation of mixed fumarates and thiol fumarates' see the whole document	9
X	CHEMICAL ABSTRACTS, vol. 77, no. 9, 28 August 1972 Columbus, Ohio, US; abstract no. 61479z, page 460; column 2; see abstract & KHIM. TEKHNOL.(KHARKOV), vol. 22, 1971 pages 3-8, N.E. KULCHITSKAYA ET AL 'production and properties of alpha-chloro-N-arylsuccinimides'	9
P,X	WO,A,94 13652 (ZENECA LIMITED) 23 June 1994 see claims	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 95/01224

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-200415	05-11-86	US-A-	4664694	12-05-87
		AU-B-	592984	01-02-90
		AU-A-	5641786	30-10-86
		JP-A-	61280485	11-12-86
FR-A-2102279	07-04-72	CH-A-	557349	31-12-74
		DE-A-	2140694	17-02-72
		GB-A-	1364284	21-08-74
		US-A-	3714175	30-01-73
WO-A-9324483	09-12-93	AU-B-	4064793	30-12-93
		BR-A-	9305532	20-12-94
		CA-A-	2109514	23-11-93
		EP-A-	0604602	06-07-94
		JP-T-	6509363	20-10-94
		US-A-	5312800	17-05-94
		ZA-A-	9303548	22-11-93
EP-A-378791	25-07-90	JP-A-	2160783	20-06-90
US-A-4956006	11-09-90	NONE		
EP-A-339390	02-11-89	JP-A-	1275578	06-11-89
		US-A-	4909828	20-03-90
WO-A-9413652	23-06-94	AU-B-	5469194	04-07-94
		CN-A-	1095066	16-11-94
		ZW-A-	15693	07-09-94